eISSN 2076-6327

IJMS International Journal of Medical Students

Year 2015 | Months Nov-Mar | Volume 3 | Issue 1 www.ijms.info

IJMS

INTERNATIONAL JOURNAL *of* MEDICAL STUDENTS

International Journal of Medical Students

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Shattered Dignity

"Breaking the Shackles: Anto's Journey" Collection
By Anto Sg (Agus Sugianto) (with authorization).
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Year 2015 - Volume 3 - Issue 1

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e-ISSN 2076-6327 (Online)

Issued in Rochester, MN, USA.

International Journal of Medical Students

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International Journal of Medical Students

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Shared Decision Making and Effective Physician-Patient Communication: The Quintessence of Patient-Centered Care

Huy Ming Lim,[1] Kristiana Siste Kurniasanti.[2]

"The good physician treats the disease; the great physician treats the patient who has the disease."

—Sir William Osler

The Institute of Medicine's (IOM) 2001 landmark report, *Crossing the Quality Chasm: A New Health System for the 21st Century*, identified patient-centeredness as one of the fundamental attributes of quality health care, alongside safety, effectiveness, timeliness, efficiency, and equity.[1] The IOM defined patient-centeredness as "providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions."[1] This concept of patient-centered care represents a paradigm shift from the traditional disease-oriented and physician-centered care, grounding health care in the subjective experience of illness and the needs and preferences of individual patients rather than the evaluation and treatment of diseases which emphasizes on leveraging clinical expertise and evidence derived from population-based studies.

A multiyear research conducted by the Picker Commonwealth Program for Patient-Centered Care (now the Picker Institute), which coined the term "patient-centered care" in 1987, revealed that patient-centered care encompasses seven dimensions from the patient perspective: (1) respect for patients' values, preferences, and expressed needs; (2) coordination and integration of care; (3) information, communication, and education; (4) physical comfort; (5) emotional support and alleviation of fear and anxiety; (6) involvement of family and friends; and (7) transition and continuity of care.[2] This conceptual framework transcends the earlier interpretations of patient-centeredness as a way of how physicians should interact and communicate with patients at the interpersonal level, expanding the concept to the health care system level.[3] Since the inception of the patient-centered care concept, a plethora of studies have repeatedly shown that orienting health care around the needs and preferences of patients holds promise for improved health care quality, patient satisfaction, and health outcomes.[4-8]

At the pinnacle of patient-centered care is shared decision making, a process by which clinicians and patients participate jointly in making health decisions for a preference-sensitive condition—a condition where more than one screening, diagnosis, intervention, or support strategy is clinically appropriate.[9,10] Shared decision making goes beyond the discussion of risks and benefits involved in the informed consent process.[11] It also helps identify and takes into consideration the patient's circumstances, values, and informed preferences for the risks, benefits, and uncertainties associated with each alternative. This is in sharp contrast to the traditional decision-making approach, in which clinicians make decisions *for* rather than *with* patients. Shared decision making recognizes that both clinicians and patients bring different but equally important forms of expertise to the table. The extent to which a clinician or a patient takes responsibility for the decision-making process varies in different circumstances along a continuum between two extremes: clinician-driven decision making and patient-driven decision making.[12]

Shared decision making is only attainable in the presence of effective physician-patient communication. In fact, quality communication within the physician-patient dyad is the single most important enabler of quality health care, without which the delivery of patient-centered care would not be possible.[13] Clear, respectful, and empathic communication between health care professionals and patients enables and supports information exchange, shared decision making, management of uncertainties and emotions, patient self-management, and meaningful clinician-patient relationship.[14] Successful integration of these functions leads to increased access to care, greater patient knowledge and shared understanding, enhanced therapeutic alliances, better management of emotions, improved family and social support, enhanced patient empowerment and agency, and higher quality health decisions, which, in turn, improve patient satisfaction, treatment adherence, physical and emotional well-being, and health outcomes.[14-18] In contrast, gaps or lapses in physician-patient communication can lead to medical errors and undesirable outcomes.[19,20]

The experience articles by DiSalvo in this issue of *International Journal of Medical Students* (IJMS) present the perspectives and experiences of a medical student with regard to patient-centered care as he engaged in the care process of patients as part of his clinical training. The first article explores the importance of patient-centered communication and shared decision making through his experience with a chronic liver failure patient.[21] The patient was loaded with physical and emotional discomforts

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owing to lapses in physician-patient communication, a deficient coordination and transition of care, and a lack of attention to the patient's physical and emotional needs. The second article discusses the significance of treating patients as individuals and incorporating patients' values and preferences into clinical practice through his reflection on the meaning of the "First, do no harm" aphorism as he followed up a critically injured patient who was unable to decide for himself.[22] In both cases, paternalistic physicians made health decisions for the patients without adequate communication with the patients or their families and friends.

DiSalvo's experiences add to the growing body of evidence that there is inadequate physician-patient communication and little shared decision making taking place in clinical practice, despite the universal recognition of patient-centered care as the desideratum of health care. Many physicians feel that they actively engage patients in the decision-making process and communicate effectively with their patients, but evidence suggests a perception-reality gap and a discrepancy between patient's and physicians' impressions about the care received or provided.[23,24] As a consequence, decades after the publication of the first compelling evidence to support patient-centered care,[25] paternalism continues to dominate health decision making, and the primacy of patients' preferences and expressed needs remains to be appreciated in most clinical encounters.[26-28]

A number of reasons may account for the limited adoption of shared decision making in clinical practice. Most clinicians cite time constraints, lack of applicability due to patient characteristics, and lack of applicability due to the clinical situation as the most important barriers to engaging patients in the decision-making process.[29] These perceived barriers likely represent misconceptions about shared decision making.[30] Current evidence indicates that implementation of shared decision making does not result in a systematic increase in consultation duration.[31] Additionally, regardless of their education and functional health literacy, all patients want to be involved in health decision making, albeit with different levels of engagement.[32] Therefore, even the most vulnerable patients should not be systematically excluded from shared decision making. Other misconceptions which hamper the implementation of shared decision making include misconceptions about the nature of shared decision making, the incompatibility of shared decision making with evidence-based practice, and the degree to which patients wish to share in decision making.[30]

In contrast to clinician-reported factors which reflect clinicians' presumptions that many patient will not benefit from shared decision making or do not wish to take part, patients reported a multitude of barriers which limit their capacity to participate in shared decision making. These patient-reported barriers include inadequate information provision, lack of continuity of care, inadequate environmental conditions, interpersonal characteristics of the clinicians, medical terminology used by clinicians, and a power imbalance in the physician-patient relationship.[33] The power imbalance between clinicians and patients causes patients to undervalue their knowledge and expertise relative to that of clinicians and adopt a passive and compliant role out of the fear of being labeled as "difficult" patients.[33,34] Additionally, patient perceptions of shared decisions may differ from physician perceptions of shared decisions.[35,36] Understanding patient perceptions of shared decision making and barriers to its implementation is particularly important, as only patient-reported shared decision making is significantly and positively associated with improved patient outcomes.[37]

While the major obstacles to the implementation of shared decision making are misconceptions about shared decision making, organizational factors, and factors associated with decision-making interactions, inadequate physician-patient communication is largely attributable to the lack of emphasis on communication skills in medical training. Most communication training takes place during the preclinical years of undergraduate medical education in the form of lectures and role plays with standardized patients. In the clerkship years, at a time when students have direct encounters with patients and communication skills are most crucial, little attention is devoted to communication training. The teaching of diagnostic skills and patient management takes the central stage. Rarely do students receive specific instruction or feedback regarding their interactions with patients. Similarly, communication skills are often not addressed in postgraduate medical training, leaving residents and practicing physicians to learn communication skills on their own. Additionally, physicians cite time pressures as a significant barrier to establishing effective communication with patients, as listening to patients, addressing their needs and emotional concerns, and helping them make decisions that are consistent with their values and preferences all require time.[38-40]

To successfully achieve the provision of patient-centered care and improve the quality of health care, critical barriers to shared decision making and effective physician-patient communication must be addressed. A number of effective interventions directed at clinicians and patients have been developed for this purpose.[41] Well-designed training programs for clinicians have been shown to be effective in transferring patient-centered skills to clinicians, leading to significant increases in the patient-centeredness of consultation processes.[42] Decision aids, on the other hand, improve patients' knowledge and risk perceptions, promote their active participation in decision making, and reduce their internal decisional conflict related to feeling uninformed and unclear about their personal values.[31] Various other patient engagement strategies have also been developed and proved to be effective in improving health literacy, helping patients make appropriate health decisions, and improving the quality of care process.[43] These findings are encouraging. Nonetheless, a genuinely patient-centered care would not be possible if power imbalances, either perceived or real, continue to exist in the physician-patient relationship. Interventions must be developed to redress these power imbalances to facilitate shared decision making and effective communication between physicians and patients.

Patient-centered care is the answer to the health care reform necessitated by today's increasingly complex and fragmented health care delivery system. A paradigm shift towards patient-centered care promises many potential gains, including improved health care quality and safety, increased patient satisfaction and adherence to treatment plans, improved health outcomes, and reduced health care cost. Regrettably, despite the ubiquitous talk about patient-centered care in modern health care, shared decision-making and effective physician-patient communication—the two cruxes of patient-centered care—are

yet to become the norms. Strategies to promote and enhance shared decision-making and effective communication between clinicians and patients should be rigorously implemented to establish a health care system that truly values patients as individuals and turn the rhetoric of patient-centered care into reality.

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Acknowledgments
None.

Conflict of Interest Statement & Funding
The Authors has no funding, financial relationships or conflicts of interest to disclose.

Cite as:
Lim HM, Kurniasanti KS. Shared Decision Making and Effective Physician-Patient Communication: The Quintessence of Patient-Centered Care. Int J Med Students. 2014 Nov-2015 Mar;3(1):7-9.

IJMS International Journal of Medical Students

Original Article

Essential Heavy Metals in Renal Tumor Tissue and Its Possible Relation to Carcinogenesis: Applying the Scanning Electron Microscopy Coupled with X-Ray Microanalysis Technique

Tânia Nogueira,[1] Mariana Semedo,[2] Elisabete Cunha.[3]

Abstract

Background: Metals such as copper and zinc are crucial in several vital functions in the human body; the absence of these metals can cause serious illness. When in excess, however, they can have toxic effects which may be associated with carcinogenesis, as is described in the literature. Thus, it is important to realize that without these essential metals in their due proportion, the human body could not maintain its proper metabolic function. **Methods:** The main goal of this paper was to compare qualitatively and semi-quantitatively the amount of both copper and zinc present in the tumor tissue (tissue from patients who had undergone partial or radical nephrectomy) and in the control tissue (which was adjacent to the tumor tissue). This study was carried out using Scanning Electron Microscopy coupled with X-Ray Microanalysis (SEM-XRM). **Results:** There is a different concentrations of copper and zinc in the samples of tumor tissue and controls that were studied. **Conclusion:** This work complements previously published results about the presence of metals in the human body and their probable influence on carcinogenesis.

Keywords: Copper, Zinc, Renal Cell Carcinoma, Scanning Electron Microscopy, Electron Probe Microanalysis (Source: MeSH-NLM).

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Introduction

The majority of the chemical elements that compose the periodic table are present in the human organism; some metals are even vital to its functioning. Their absence can create deficiencies in metabolic functions, leading to serious illnesses, while their excessive abundance can be toxic. Copper (Cu) and zinc (Zn), along with other heavy metals, are involved in metabolic processes which regulate energy production. However, despite the fact that they are essential, their high levels cause a toxic effect which can ultimately lead to carcinogenesis. Thus, the aim of this work was to compare the chemical content of these metals in tumor tissue and control tissue (adjacent to the tumor).

Copper (Cu) deficiency is a rare condition in human beings since almost all diets have at least some quantity of this metal and it is essential in low doses only (the recommended value is 0.9mg per day).[1] Non-occupational exposure is through ingestion but populations can also be exposed by inhalation or skin contact since copper can be found in surface waters due to the increasing utilization of the element in aquaculture to control algae and pathogens.[2]

Previous studies showed that in individuals who smoke, there is a higher level of plasmatic Cu; similar findings occur in patients with arteriosclerosis and in patients with periphery arterial disease.[3-5] Despite all of these considerations, it is in the study of tumors that the Cu dosage has more interest as its concentrations have been proven to be higher in renal clear-cell carcinoma samples, contrarily to what occurs in liver tumors.[6] Therefore, this metal was chosen to study since it is essential to consider the problems related to the ingestion, absorption, and transport of Cu in the blood stream, and the resultant possible toxic effects associated with Cu.

The primary toxic effects of Cu manifest in the liver as this is the organ where Cu accumulates after entering circulation. However, one of the most studied illnesses caused by these toxic effects is cancer since it results from a series of molecular events that change the normal cell properties. This also happens when cells are exposed to elevated levels of heavy metals as these are susceptible to redox reactions, consequently promoting the formation of reactive oxygen species (ROS). Some research has already attributed Cu toxicity to a propensity for its ions to contribute to the development of ROS, a process that transforms the structure and/or function of crucial molecules.[1] Hence, this relationship is vital in order to understand carcinogenesis as a result of excessive exposure to metals since excess Cu can also induce oxidative stress by decreasing glutathione levels.[7] Thus, it can be concluded that even if Cu is essential to the functioning of the human organism, it brings about problems when it is deficient and it can also lead to toxicities when in excess that could induce carcinogenesis.

Zinc (Zn) compounds exist in many objects as they are widely used by the pharmaceutical industry.[8] This metal is essential not only for humans but for all living organisms as it is a constituent of about 300 enzymes and even more proteins. As a result, it plays a central role in human health given that there are numerous biological processes that require the sufficient availability

Submission: Aug 9, 2014
Acceptance: Jan 19, 2015
Publication: Feb 8, 2015
Process: Peer-reviewed

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of zinc.[9] There is no stored form of Zn in the human body;[10] it is hypothesized that the total amount of Zn in the body is 2 to 4g and the recommended daily values are approximately 8 to 11mg in the United States and 9.4 to 10mg in Europe.[11]

This heavy metal is also essential for the normal functioning of the immunological system and for infantile development since a deficiency in this metal is a limiting factor for growth.[12] It is important for immuno-competence and it is responsible for maintaining both macrophage and neutrophil functions, as well as for the activation of natural killer cells and the phagocytic function of granulocytes.[13] When this element is deficient, the mucosal barrier in the gastrointestinal tract and pulmonary tract is compromised, increasing the susceptibility to infections.[9] A deficiency in Zn can also emerge in individuals who suffer from inflammatory diseases of the small intestine, renal disease, burns, and some forms of cancer, among others.[13,14] Although the precise role of Zn in the regulation of apoptosis is not yet fully known, one of the origins for the loss of immunological responses is the increase in apoptosis regulated by Zn.[13] Some researches have shown that Zn can either be pro- or anti-apoptotic (depending on the concentration) and that both the deprivation and excess of this element could induce an apoptotic event in the same cell line.[9]

Metallotheionins are zinc-binding proteins and play relevant roles in Zn-mediated immunological processes; they also act as a cellular defense against partially reduced oxygen.[13] A large number of studies have established that Zn inhibits the phagocytosis and reduces the discharge of oxyradicals and the production of superoxide and hydrogen peroxide.[13] However, there could even be an increase in ROS due to a G-protein coupled system activated by Zn.[13] Moreover, the dislocation of this metal from zinc-binding structures (for example, finger structures in DNA repair enzymes) may be even be a more important mechanism in carcinogenesis compared to other metals that have well-described carcinogenic roles.[9] A rather explored example of the involvement of Zn in cancer development is prostate cancer.[9]

It should be noted that Zn is one of the trace elements that participates in the foremost biological functions, depending on a complex and precise homeostatic control, on both cellular and systemic levels. Thus, its importance to the human organism is what made it an appropriate choice for discussion in this study. Nevertheless, as previously mentioned, humans do not possess any Zn stores; as a result, the dietary acquisition of this element is essential. The toxicity is rare and exceptionally fatal; however, on the other hand, the scarcity is quite frequent, especially in individuals with alimentary restrictions or chronic diseases. Based on this, Zn consumption must be in the ideal proportions as high levels of Zn can lead to carcinogenesis.

In summary, the main goal of this study is to investigate the presence or absence of these two heavy metals in samples of renal tumor tissue and to compare these levels to adjacent normal renal tissue.

Methods

Given that the renal tumor is the most well described tumor related to the exposure to heavy metals, several samples of tumor and control tissue were collected from the kidneys of seven patients (one female and six males; ages ranging from 46 to 78 years old) that were submitted for radical or partial nephrectomy. These samples were studied and compared in their chemical composition for the essential metals copper and zinc. This study was approved by the local ethics committee of Centro Hospitalar de S. João, E.P.E. and patient consent was obtained from all participants.

Electron microscopy allows the observation and characterization of large surfaces in thick samples as well as the characterization of the qualitative and semi-quantitative aspects of their chemical content. In this investigation, the Scanning Electron Microscopy was coupled to X-Ray Microanalysis (SEM-XRM); this enabled images to be obtained with magnifications ranging from 10X to 500 000X. A JEOL-6301F coupled with Noren Voyager X-ray with EDS (Energy Dispersive Spectrometry) detection system was used with which it was possible to detect the presence of different heavy metals in the samples if they had a concentration above 0.2-0.3%. The samples were prepared by following an adapted protocol from Cunha et al. where the samples were fixed in a 3% glutaraldehyde solution and subsequently dehydrated in ethanol and critical point-dried in a Balzer´s apparatus.[15] The preparation was mounted on metal stubs and coated by carbon under a vacuum.

To our knowledge, this technique has not been used before to study the presence or absence of heavy metals in tumor tissue. This process allows one to qualitatively identify all the metals that are on the surface of the tissue. Among all of the elements detected, Cu and Zn were chosen for study because even though they are heavy metals (and thus usually considered maleficent), they are also essential to the functioning of the human organism in the appropriate concentrations, as previously mentioned.

By using the SEM-XRM technique it was possible to obtain microanalysis spectrums (qualitative and semi-quantitative) of the focused zones due to backscattered electrons, and the topographic visualization of the tissue surface due to secondary electrons. First, all the samples (tumor tissue and control samples) were processed using secondary electrons which allowed for the visualization of white spots that corresponded to the deposition of heavy metals (particles with high molecular weight) in tumor tissue samples. Then, the identification of these heavy metals in all of the opaque inclusions was made by the screening of the spots with X-ray elemental microanalysis in order to determine which of them contained heavy particles. Thus, this innovative technique allowed for the in situ identification of heavy metal particles.

Despite the limited number of patients, it was possible to test the association between the tumor and control tissues and the presence or absence of Zn and Cu using the Pearson's Chi-squared test in the R statistical software (R Development Core Team, 2011).

Results

The patients in the study had three different types of renal cancer: clear-cell carcinoma (6 patients), and adenoma and papillary cell carcinoma (both in one patient but in two different pieces that were collected from the same kidney).

The results obtained demonstrate that the chemical composition of Cu and Zn in the tumor tissue (***Figure 2A*** and ***Figure 2B***) is different from the one in the control tissue (***Figure 1A*** and

Figure 1B) (2 = 10.285, df = 1, p-value = 0.0013). It was verified that Cu and Zn were present in the tumor tissue (***Figure 2C***) but not in the control tissue (***Figure 1C***).

The tumor tissue and the control tissue differed in their chemical composition, especially regarding the accumulation of Cu and Zn in the spot marked as Z4 in ***Figure 2B***, which is from the tumor tissue itself. In the following graphics, there is no Cu and Zn spike from the X-Ray Microanalysis in the control sample, corresponding to ***Figure 1C*** (performed in the spot marked as Z2 in ***Figure 1B***). This is contrary to Figure 2C where the spike can be seen. The control sample did not have these heavy metals, at least in concentrations higher than 0.2-0.3% in mass, which was not the case in the tumor samples where these heavy metals were detected.

Discussion

There are numerous essential metals, including Cu and Zn, required for the necessary functioning of living organisms. However, even though they are essential for biological functions, they can become toxic in high levels. Heavy metals pose the most concern for human health because they can easily accumulate in the organism. Cadmium (Cd), mercury (Hg), lead (Pb), arsenic (As), and chromium (Cr) have already been described and classified as carcinogenic.[16]

It is vital that the equilibrium is maintained between free radical production and antioxidant defenses as free radicals are related to the promotion of carcinogenesis by modifying DNA and even altering the cellular antioxidant defense system.[17] When the balance tends to favor the generation of these radicals, the organism is in oxidative stress where lipids, proteins, and DNA become oxidized, inhibiting their normal function and leading to several pathologies, including cancer.[18]

Currently, cancer is one of the diseases that affects a significant portion of the population and it represents a major concern to worldwide health systems. Cancer cells have different features depending on the type of tumor involved; this allows them to grow and metastasize to other organs. Tumor cells grow more rapidly than healthy cells, which is the reason that this disease spreads so quickly throughout the body. In most carcinoma types, there is a previous inflammatory disease that exists prior to the malign alteration. In other cancer types, an oncogenic alteration induces an inflammatory microenvironment that promotes tumor development. In 2008, Mantovani et al. published an article stating that cellular inflammatory mediators are important constituents of a tumor's local environment.18 Thus, when present, the inflammation processes help promote proliferation and tumor cell survival in addition to facilitating metastasis.[18]

The main goal of this investigation was to compare qualitatively the chemical content of both Cu and Zn in renal tumors and control tissue using the SEM-XRM technique. The results demonstrate that these heavy metals are present in tumor tissue but absent in control tissue (normal tissue adjacent to the tumor). Therefore, the results support a notion previously postulated by Brys et al. and Ogunlewe et al. where different metals in high levels, whether essential or not, are related to multi-organ carcinogenesis.[18,19] In addition, Hardell et al., con-

Figure 1A. Secondary Electron Image from Control Renal Tissue. Magnification at 4000x.

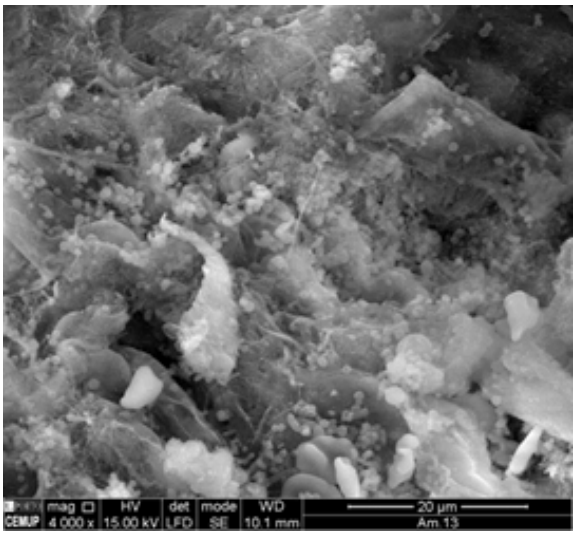


Figure 1B. Backscattered Electrons Image from Control Renal Tissue. Z2 Corresponds to the Zone where the Chemical Composition was Obtained by X-Ray Microanalysis. Magnification at 4000x.

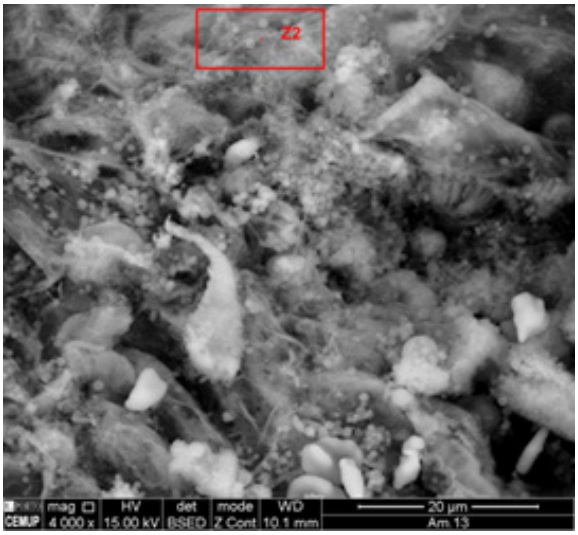
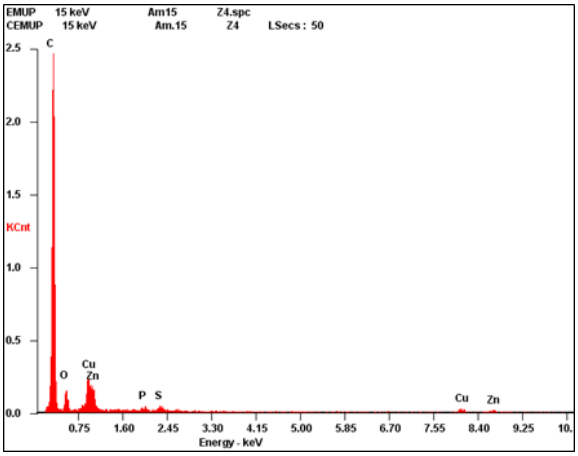


Figure 1C. X-Ray Microanalysis (XRM) Spectrum Showing the Absence of Metals and the Presence of Normal Elements in Control Renal Tissue (Carbon (C), Nitrogen (N), Oxygen (O), Sodium (Na), and Sulfur (S) in the Analyzed Zone Marked as Z2 in Figure 1B.



cluded that there is an increase in Cd, Zn, and Cu levels in kidneys that have cancer cells.[20] Moreover, in 2013 Pirincci et al., detected high levels of Pb in renal carcinoma patients.[21] However, contrary to these findings, Fassina et al., demonstrated a significant decrease in Cd and Zn concentrations in all of their studied neoplastic tissues of renal cell carcinoma.[22] Karcioglu et al., showed that Cd is not found in tumor samples but it is normally present in kidney tubular cells. This study reported that Zn and Cu proportions are reduced in renal tumor tissues.[23] Furthermore, Dobrowolski et al. reported low concentrations of Cd in renal cell carcinoma and low concentrations of Pb in the cortex of cancerous kidneys.[24] A few years later, Cerulli et al. observed the presence of low concentrations of Cd but high Pb levels in excised tumor tissue with elevated levels of both of these two metals in the adjacent (normal) tissue.[25] Importantly, the technique that was used in our study had not been used in the other related studies.

Although renal cancer is the most widely studied cancer related to heavy metal exposure, research has also examined heavy metal exposures in other types of cancer. Namely, in 2003 Waisberg et al. published a study demonstrating lung carcinoma induction when exposed to Cd.[26] In 2012, Natalie et al., discovered that the chronic exposure to Cd could also lead to breast cancer.[27] In addition, a study examined the association between Zn intake (as a supplement) and prostate cancer risk, in which they observed 2901 new cases of prostate cancer in 14 years.[9] The risk of prostate cancer was found to be increased by the long-term supplementation of Zn with doses higher than 100 mg/day. This may not, however, be a result of the direct carcinogenicity of this metal, but rather explained by the immunosuppression provoked by the high doses of Zn.[9]

If our results could be confirmed by future studies, the hypothesis that heavy metals could be the cause or the consequence of the carcinoma could be further clarified. Namely, additional research may provide an answer to the question of whether these elements could be used as biomarkers with prognostic or diagnostic implications in clinical practice.

As is evident, the precise relationship between heavy metals and carcinoma is controversial and ambiguous. It is known and well described that heavy metals are involved in the carcinogenesis; this fact is widely supported in various publications. Our study is intended to highlight the presence of the essential metals Cu and Zn in tumor tissue, likely due to their accumulation over time as an anomalous sequestration of these heavy metals. However, the technique used to study these metals may be seen as a limitation as it is qualitative and only semi-quantitative.

Heavy metals are suspected to be a risk factor for the development of malignancy. But, at this time, it is unclear if these elements are either the cause or the consequence of the cancer or if they are involved in carcinogenic pathways. This work complements previous findings examining the possible relationship of essential heavy metals with carcinogenesis.

Figure 2A. Secondary Electron Image from Renal Tumor Tissue. Magnification at 4000x.

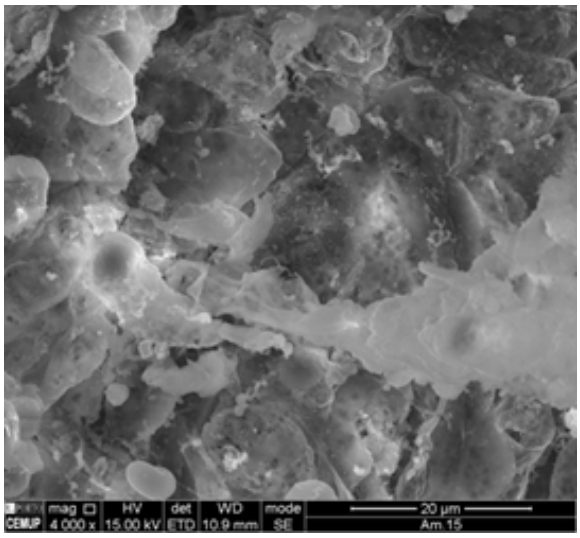


Figure 2B. Backscattered Electrons Image from Renal Tumor Tissue. Z4 Corresponds to the Zone where the Chemical Composition was Obtained by X-Ray Microanalysis. Magnification at 4000x.

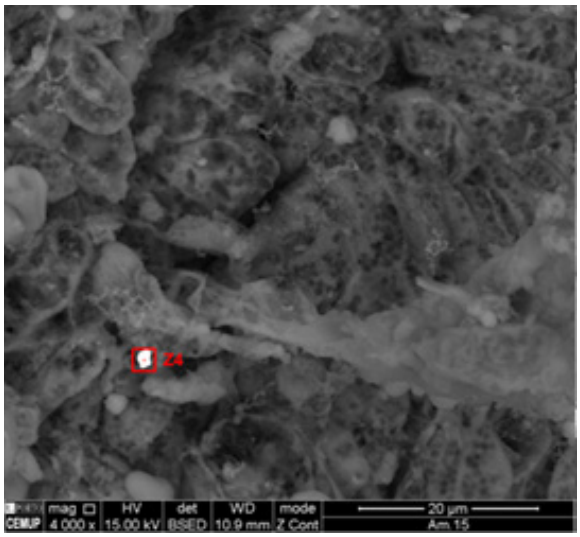
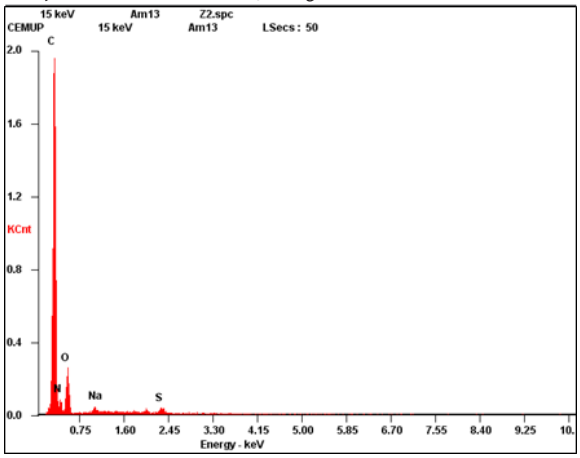


Figure 2C. X-Ray Microanalysis (XRM) Spectrum Showing the Presence of Copper (Cu) and Zinc (Zn) in Renal Tumor Tissue in the Analyzed Zone Marked as Z4 in Figure 2B.



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Acknowledgments
None.

Conflict of Interest Statement & Funding
The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea: TN, MS, EC. Collect data/obtaining results: TN, MS. Analysis and interpretation of data: TN, MS, EC. Write the manuscript: TN. Critical revision of the manuscript: EC. Approval of the final version: EC. Contribution of patients or study material: EC. Obtaining financing: EC.

Cite as:
Nogueira T, Semedo M, Cunha E. Essential Heavy Metals in Renal Tumor Tissue and Its Possible Relation to Carcinogenesis: Applying the Scanning Electron Microscopy Coupled with X-Ray Microanalysis Technique. Int J Med Students. 2014 Nov-2015 Mar;3(1):10-4.

Lifesaving Sonography Protocols: A Pilot Course Involving Undergraduate Medical Students

Jakub Wisniewski,[1] Hanna Garnier.[1]

Abstract

Background: Ultrasonography protocols are easy to learn, frequently used in emergency medicine, and could be useful for inexperienced doctors. In this field, only a few protocols are needed to give an initial diagnosis and to start fast and proper treatment. Until now, only Focused Assessment with Sonography for Trauma (FAST) protocol training studies have been reported in the medical literature. Our point-of-care course, comprised of extended FAST, lung scan and ocular scan trainings. The students' curriculum usually does not include such ultrasonography courses, thus, we wanted to check its utility for the undergraduate medical students. **Methods:** Training lasted six days and consisted of two parts: 22 hours of theoretical classes and 18 hours of practical activities, all trained and evaluated by six experienced medical doctors. Eighty-five elected students completed pre- and post-study questionnaires about emergency ultrasonography and passed the practical final exam. **Results:** Eighty-five participants of the course were present in the pre- and final test. Final test scores of theoretical and practical exams were significantly higher after the training (58% vs. 87%; n=85; p<0.01). Answers for the questions related to FAST and EFAST (extended FAST) were correct irrespective of completion of the course. A question regarding the sonographic evaluation of body fluid incontinence was found to be the most difficult for students. After the course, 96.5% of participants were able to complete an EFAST scan at an adequate level of performance in under two minutes. **Conclusion:** Results show that medical students significantly extended their knowledge about point-of-care emergency medicine ultrasonography and acquired practical skills during the course. Emergency medicine ultrasonography courses could be included into medical students' curricula.

Keywords: Ultrasonography; Education, Medical, Undergraduate; Education, Medical; Students, Medical (Source: MeSH-NLM).

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Introduction

Medical students' education does not contain regular courses in ultrasonography; this is an easily available, risk-free, and non-invasive imaging method. Ultrasonography becomes a part of the basic patient examination (such as observation, palpation, and auscultation). Therefore, we often call it "a modern stethoscope".[1]

Ultrasound examination and its correct interpretation require significant training and a lot of experience.[2] However, in emergency medicine (EM), only a few protocols are needed to give an initial diagnosis and to start proper treatment. The most common protocol in the EM is Focus Assessment with Sonography for Trauma (FAST), which is only one part of the full ultrasound (US) examination. It gives a fast and accurate evaluation of the hemorrhage in the peritoneal cavity.[3] Though adding ultrasonography to the students' curriculum seems to be time-consuming, it is proven that only two days (16 hours) of the course are needed to complete a correct FAST.[4] Additionally, ultrasound examination of the eye (which allows for the rapid assessment of the cerebral edema) is easy enough to be taught and used by non-expert operators on the International Space Station (ISS).[5,6]

To date, there is an increasing number of ultrasound teaching pilot studies. These kinds of activities, used as a supplement to gross anatomy courses, are beneficial even during the first years of study.[7] Many studies show that teaching ultrasonography to 3rd, 4th, and 5th year students can effectively support and develop their clinical knowledge.[8-11] Ultrasonography use in EM seems to be one of the most important aspects. Some academics do not realize how important it can be in giving the prompt diagnosis, especially for the young doctors, who are still lacking experience. Ultrasonography allows fast clinical assessment of dehydration or can yield a prompt pneumothorax diagnosis.[12,13] Until now, only FAST training studies have been reported in the medical literature.[14] Our point-of-care course, included extended FAST, lung scan and ocular scan training.

We assumed that teaching easy protocols with brief training periods may be successfully included in the students' curriculum. The aim of our study was to check the effectiveness of the six-days course in EM for the medical students of the Medical University of Gdansk, Poland.

Methods

We conducted a six-days facultative course teaching about extended FAST (EFAST), Bedside Lung Ultrasound in Emergency (BLUE), Focus Assessed Transthoracic Echocardiography (FATE), monitoring of central venous access, ocular ultrasound in trauma and sonographic estimation of body fluid status assessment (***Table 1***). The training was held at the Medical University of Gdansk, Poland from October until November 2014.

Ninety-seven medical students of the University were voluntarily enrolled and they were requested to complete the pre-question-

Submission: Jan 10, 2015
Acceptance: Mar 29, 2015
Publication: Mar 31, 2015
Process: Peer-reviewed

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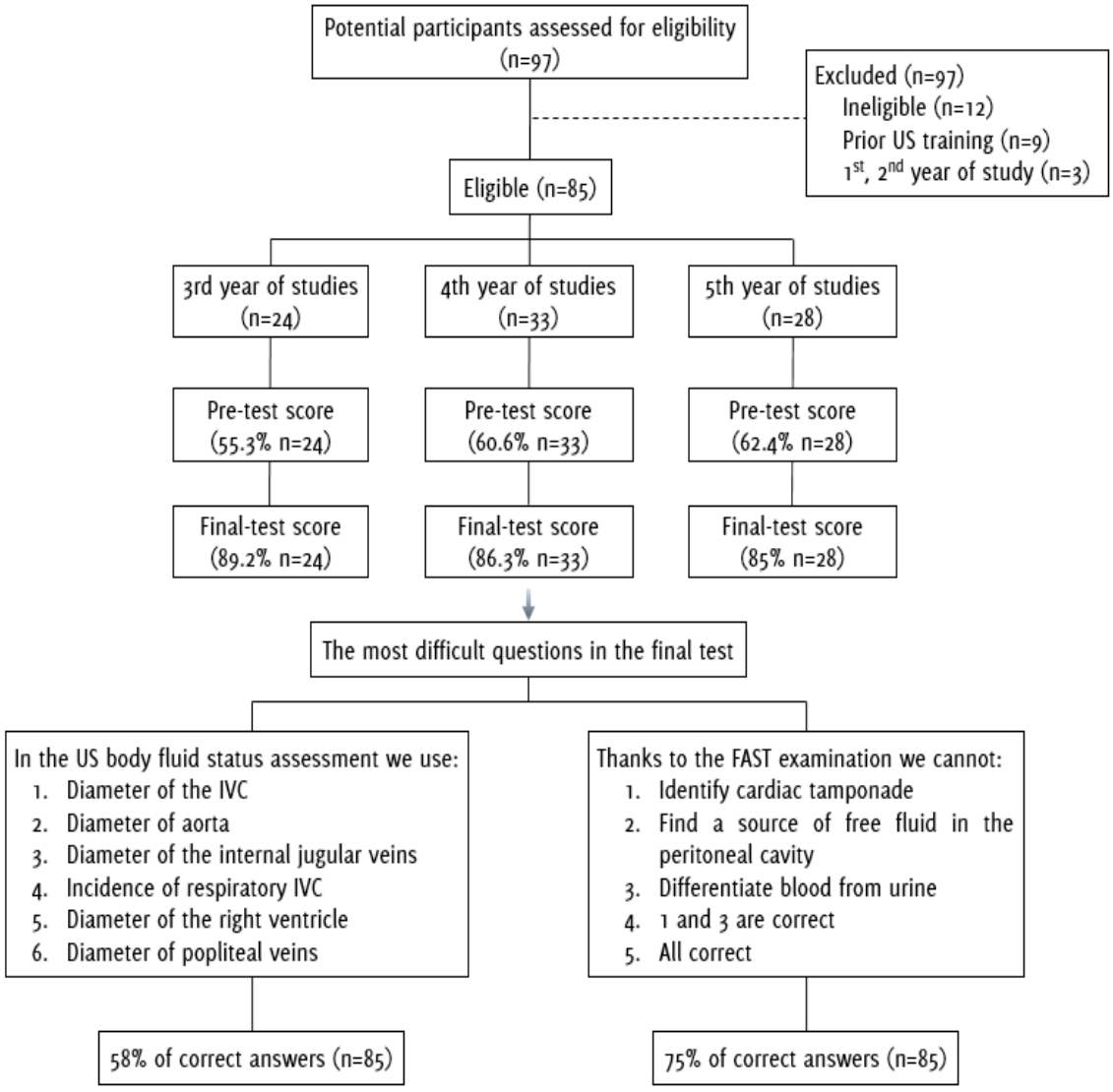
Figure 1. Flow Diagram Showing Characteristics of the Study.



Legend: US - Ultrasound; IVC - inferior vena cava; FAST – Focused Assessment with Sonography for Trauma.

naire asking about their personal data and their previous experience with ultrasonography. Eighty-five from the 3rd, 4th, and 5th years of study with no prior US course (inclusion criteria) were divided into four equal groups for the theoretical classes (***Figure 1***). Twelve students in the 1st and 2nd years of study or those with the prior US training were excluded. They were not informed about the course program in advance. Subsequently, each group was divided into four teams for practical training. We prepared a comprehensive, 6-days course for the medical students, focused on the use of an ultrasound in EM. The course consisted of two parts, 22 hours of the theoretical classes and 18 hours of the practical activities, all trained and evaluated by six experienced medical doctors. Before the course, students completed a multiple choice test of 25 questions about the practical use of ultrasound in EM. Eleven questions from the test involved knowledge about EFAST/FAST, five about ocular ultrasound in trauma, and five about BLUE. The same test was held after the course.

We analyzed all of the results from both of the tests (pre- and post-course) using a paired samples t-test and a 99% confidence interval (CI=99%). Statistical analyses were run using the STATISTICA 10 software (StatSoft Inc, Tulsa, OK).

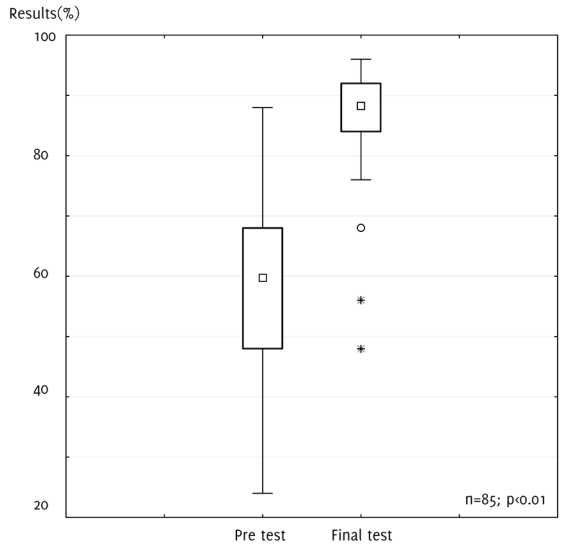
After theoretical classes, students were working at cart-based ultrasonography machines (GE Logiq 7 and Philips: Sparq, ClearView, CX50, iU22). All of them were taught how to perform a proper EFAST, BLUE, FATE, and Ocular protocols. This part was evaluated by the practical test (EFAST scan completed in less than two minutes).

Results

Eighty-five participants in the course (23 from the 3rd, 35 from the 4th and 27 from the 5th year) participated in the pre- and final test.

The pretest mean scores of the students from the 3rd, 4th, and 5th years were 56% (n=24), 61% (n=33), and 62% (n=28), respectively. The mean scores of the final test of the students from the 3rd, 4th, and 5th years were 89% (n=24), 86% (n=33), and 85% (n=28), respectively. There was no statistically significant differences between the scores of the students from the different years (pretest p=0.32; final test p=0.47). The total

Figure 2. Comparison of the Pre And Final Test Results



Legend: Data are presented as median (central square), 25–75% (top and bottom of boxes). Top bar represents 1,5 of the highest interquartile range (IQR). Bottom bar represents 1,5 of the lowest IQR. The dot represents the middle outlier; stars represent two extreme outliers.

Table 1. Course Schedule

Day	Topic
First (Saturday)	1. From FAST* to ABCD ultrasound – introduction. 2. US** in emergency medicine – for and against. 3. I have an ultrasound equipment, what's next? Knobology. 4. FAST 5. E-FAST*** 6. US and a central venous access. 7. Polytrauma – ultrasongraphic diagnostic 8. Patient in shock – ultrasonographic diagnostic 9. Practical activities.
Second (Monday)	1. Hydratation rating – how to use ultrasound. 2. Practical activities.
Third (Tuesday)	1. Other practical aspects of the US use in emergency medicine. 2. Practical activities.
Fourth (Wednesday)	1. BLUE† protocol. 2. Practical activities.
Fifth (Thursday)	1. FATE‡ 2. Practical activities.
Sixth (Friday)	1. Final test. 2. Case presentation. 3. Discussion. 4. Literature overview. 5. Practical exam.

Legend: *Focused Assessment with Sonography for Trauma; **Ultrasonography; ***extended-FAST; †Bedside Lung US in Emergency; ‡Focus Assessed Transthoracic Echocardiography.

mean final score (86%; n=85) was significantly higher ($p<0.01$; at statistical significance of level 0.01) than the mean result before the course (59.7%; n=85) (***Figure 2***).

We found that most of the answers to the questions associated with FAST and EFAST were answered correctly irrespective of completion of the course. A question regarding the sonographic evaluation of body fluid incontinence turned out to be the most difficult. The second most difficult questioin was about the usage of the EFAST examination. After the course, 96,5% (82/85) of participants completed an EFAST scan at an adequate level of performance in under two minutes.

Discussion

Our six-days, intensive, point-of-care ultrasound course in EM turned out to be effective. Results showed that medical students significantly extended their knowledge about point-of-care EM US and acquired practical skills during the course. We can conclude that integrating emergency ultrasonography classes into medical school curriculum should be taken into consideration.

The pre-test results showed that students had elementary knowledge about ultrasonography before the course (acquired during radiology or emergency medicine classes). It suggests that the point-of-care ultrasound courses could be recommended as an additional training tool which helps to order and supplement the students' knowledge.

Ultrasonography, being an inexpensive and easy-to-use tool, can also be a "modern stethoscope" during daily ward rounds. It can have a particular importance, especially in the places where elderly staff have a skeptical opinion about the use of ultrasound in daily practice. More than 6% of the patients delivered to the emergency rooms are diagnosed with pneumothorax,[15] and this diagnosis can be confirmed and localized with comparable efficacy to Computed Tomography in less than four minutes using ultrasound.[16,17] This contributes to modernization and improvement in the hospital departments.

Regardless of numerous reports concerning the usefulness of ultrasonography in different educational stages, from studying anatomy support up to elderly medical students' education, it is still has not been entered into the curriculum.[18] We need more studies (especially prospective) describing the effects of integrated ultrasonographic courses on the clinical practice. Medicine as a rapidly-developing science should pay attention, especially to the constant actualization of the students' curriculum. Thanks to this, young doctors will be able to skillfully use their medical knowledge in their future work.

The point-of-care ultrasound course has been added to the facultative curriculum at our University. Although, further research with longer follow-up should be done, in order to enhance the results and conclusions. According to the Kirkpatrick educational levels, we have evaluated our intervention at the level 2 (change in knowledge). To recommend change in the medical curriculum (which is already overcrowded), it would be necessary to reach at least level 3 evidence (change in behaviour or ability). A longer follow-up could help this stydy reach that level.[19]

Special guidelines are needed to unify both, the theoretical and practical training. There are no such instructions thus far. This is a limitation of our study; although we believe that Ultrasound Associations, such as European Federation of Societies for Ultrasound and Biology (EFSUMB; http://www.efsumb.org/) will publish adequate guidelines. That would help to create repeatable courses and would allow for the comparison of results from different universities in the world. Thus, further research should be done in order to determine whether our conclusions are correct across the globe..

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Acknowledgments

We would like to thank Wojciech Kosiak MD, PhD and Tomasz Batko MD, PhD from the Departments of Paediatrics, Haematology, Oncology, and Endocrinology in the Medical University of Gdansk for organization of the course. We also thank Blazej Littwin MD, Andrzej Pomiecko and Marcin Gajewski for their invaluable support.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conception and design the work/idea, Collect data/obtaining results, Analysis and interpretation of data, Critical revision of the manuscript, Approval of the final version: JW, HG. Write the manuscript: JW. Statistical advice, Administrative or technical advice: HG.

Cite as:

Wisniewski J, Garnier H. Lifesaving Sonography Protocols: A Pilot Course Involving Undergraduate Medical Students. Int J Med Students. 2014 Nov-2015 Mar;3(1):15-8.

Frequency of Congenital Anomalies in Newborns and Its Relation to Maternal Health in a Tertiary Care Hospital in Peshawar, Pakistan

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Abstract

Background: Congenital anomalies are a major cause of perinatal and neonatal deaths, both in low- and high-income countries. They are relatively common worldwide, affecting 3% to 5% of live births. **Methods:** A cross-sectional study was conducted from January 2014 to June 2014 at the Khyber teaching hospital in Peshawar. Specific patient information was obtained from patient records at the beginning of the study. Those individuals found to have at least one birth defect were approached and their attendants (mothers) were interviewed. Information regarding various risk factors was collected. Descriptive analyses were carried out. **Results:** Out of 1062 deliveries, 2.9% (31) of newborns had various congenital anomalies. Hydrocephalus (22.6%), anencephaly (12.9%), and spina bifida (9.7%) were major anomalies. The maternal age ranged from 18 years to 46 years (mean: 30 ± 8). Most of the anomalies (35.5%) were present in the 26-30 years age group. Out of 31 babies, 6.4% had multiple anomalies. The preponderance of various congenital anomalies was seen in parity 1 (35.4%); parities 2 to 4 had lower incidences (35.4%). The consanguinity rate was 67.7%; only 32.3% of patients were using folic acid. History of passive smoking was positive in 16.1% of cases. **Conclusion:** Anencephaly and hydrocephalus were the most prominent anomaly detected; early prenatal diagnosis may be helpful in decreasing mortality by offering early termination. Low intake of folic acid and a high consanguinity rate were the most common associated risk factors for congenital anomalies. These risk factors may be reduced by creating awareness regarding the avoidance of consanguineous marriage and promoting the use of folic acid during pregnancy.

Keywords: Congenital Abnormalities, Nervous System Malformations, Neural tube defects, Folic acid, Consanguinity (Source: MeSH-NLM).

Introduction

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Boygle defines a birth defect in his study as abnormalities of structure and function or metabolism that are present at birth and result in physical, mental disability, and even mortality.[1] Birth defects represent a prenatal origin of disorders that can be caused by a defect in a gene, chromosomal disorders, environmental teratogens, and micronutrient deficiencies. Rubella, diabetes mellitus, folic acid and iodine deficiency, medicinal and recreational drug exposure including tobacco and alcohol, and certain environmental chemicals and radiation are all other factors that cause birth defects (World Health Organization, Available from: http://apps.who.int/gb/ebwha/pdf_files/EB126/B126_10-en.pdf, updated 2015 March 3; cited 2015 March 11).

The rapid decline in infant mortality and morbidity in high-income countries has focused the attention of pediatricians to the problem of congenital anomalies. In the past, the causes of infant mortality were primarily related to infectious diseases. This tendency has been transmuted by antibodies and advances in the field of preventative medicine and immunology such that death in infancy is now more commonly due to congenital anomalies (CAs).[2] CAs are a major cause of perinatal and neonatal death in low- to high-income countries.

Each year, 7.9 million children (6% of total births worldwide) are born with a serious anomaly of hereditary origin.[3] In the United States (US), CAs are reported at a prevalence of 3% to 5% of live-births;[2] the prevalence in Europe is reported as 2.1% (EUROCAT, European Network of Congenital Anomaly Registers, Available from: http://www.eurocat-network.eu/, updated 2015; cited 2015 Jan 17). In India, congenital anomalies account for 8% to 15% of perinatal deaths and 13% to 16% of neonatal deaths.[4]

In Pakistan, approximately 6% to 9% of perinatal deaths are attributed to congenital malformations.[5] Of these, approximately 40% to 60% of congenital anomalies are of unknown etiology, 20% are attributed to a combination of heredity and other factors, 7.5% are attributed to single gene mutations, 6% are caused by chromosomal abnormalities, and another 5% are due to maternal illnesses such diabetes mellitus or infection.[6] Furthermore, low socio-economic status and low literacy rate are other components of high significance in a population.[7]

Since there have been no recent studies evaluating congenital anomalies in Peshawar, our aim is to discover the frequency of various congenital abnormalities in neonates born at Khyber teaching hospital in Peshawar. An additional aim of the study is to elicit CA associations with various risk factors.

Submission: Jan 17, 2015
Acceptance: Mar 9, 2015
Publication: Mar 24, 2015
Process: Peer-reviewed

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Methods

A descriptive, cross-sectional study was conducted at the Obstetrics and Gynecology Department at Khyber Teaching Hospital in Peshawar, Pakistan from January 2014 to May 2014. Khyber Teaching Hospital is a tertiary care hospital in Peshawar that attends to the Khyber Pukhtoonkwa Province's population. In our study, we included all those infants who were diagnosed with at least one birth defect. Information regarding patients was obtained from patient records at the beginning of the study. Mothers of all those infants with congenital anomalies were approached and interviewed and information regarding various risk factors was collected on a pre-designed pro forma. Similar to a previous study,13 the questionnaire was divided into four sections: The first section of our questionnaire included the demographic data of the child while the second part dealt with the medical history of the child's parents which included comorbidities, gestational age, gestational period, paternal age, and occupation and education level of the mother. The third part of the questionnaire consisted of a series of yes/no questions regarding various risk factor exposures. Finally, the last section identified the specific CA.

Statistical analysis was performed using the Statistical Package for Social Science (SPSS©) version 20. Continuous data was displayed as the mean ± standard deviation (SD), while the categorical and nominal data were presented as frequencies and percentages.

The Ethical Review Board of Rehman Medical College in Peshawar, Pakistan approved the study on 1st January 2014. The guidelines of the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist was followed in creating the present article.[8]

Results

Out of 1062 deliveries, 31 (2.9%) newborns had various congenital anomalies. Hydrocephalus (22.6%), anencephaly (12.9%), spina bifida (9.7%), meningocele (6.5%), microcephaly (6.5%), and cleft lip (6.5%) were the commonest congenital anomalies. The distribution of the various congenital anomalies is shown in ***Table 1***.

Out of 31 newborns, 29 (93.5%) had single anomalies and two (6.4%) had multiple anomalies. Seventeen (54.8%) were male and 14 (45.2%) were female (p=0.29). The maternal age ranged from 18 years to 46 years with a mean of 30±8 years. The majority of the anomalies (35.5%) were present in the age group of 26-30 years. The majority of the newborns (77.6%) had birth weights in the range of 2.4 to 4 kg. The consanguinity rate was 67.7%; only 32.3% of mothers were taking folic acid. Three (9.6%) patients were on treatment for diabetes mellitus (1 on insulin and 2 on oral hypoglycemic medications), and two (6.4%) patients were being treated for hypertension. A history of passive smoking was positive in five (16.1%) cases (***Table 2***).

In terms of the maternal gravida status, 6 (19.3%) mothers were primigravida, 22 (70.9%) mothers were multi gravida, and 3 (9.6%) mothers were grand-multi gravida. The proportion of various congenital anomalies in parity 1 was 35.4% and the proportion of anomalies in parities 2 to 4 was 35.4% (***Table 3***).

Table 1. Distribution of Congenital Malformations in Newborns.

Congenital anomalies	Frequency (n=31)	%
Hydrocephalous	7	22.6%
Anencephaly	4	12.9%
Spina bifida	3	9.7%
Meningocele	2	6.5%
Microcephaly	2	6.5%
Cleft lip	2	6.5%
Ambiguous genitalia	1	3.2%
Dilated abdomen	1	3.2%
Duodenal atresia	1	3.2%
Dyonophic, dilated abdomen	1	3.2%
Gastrochiasis	1	3.2%
Hydrocele/kidney not palpable	1	3.2%
Meningomycele	1	3.2%
Spina bifida,cleft lip, palette	1	3.2%
Telepies aquina varacele	1	3.2%
Telepies left foot	1	3.2%

Table 2. Demographic Details and Major Characteristics.

Characteristics	Frequency (n=31)	%
Newborn Weight		
1-2.4kg	7	22.6%
2.5-4kg	24	77.6%
>4kg	0	0%
Newborn Sex		
Male	17	54.8%
Female	14	45.2%
Maternal Age		
15-20	3	9.7%
21-25	5	16.1%
26-30	11	35.5%
31-35	4	12.9%
36-40	2	6.5%
>40	6	19.4%
Paternal Age		
20-25	8	25.8%
26-30	8	25.8%
31-35	6	19.4%
36-40	2	6.5%
>40	7	22.6%
Consanguinity		
Yes	21	67.7%
No	10	32.3%
Folic acid use		
Yes	10	32.3%
No	21	67.7%
Smoking History		
Yes	0	0%
No	26	83.9%
Passive	5	16.1%

Table 3. Maternal Parity.

Parity	Frequency (n=31)	%
0	3	9.7%
1	11	35.5%
2-4	11	35.5%
5 or more	6	19.4%
Total	31	100%

Discussion

Major CAs occur in approximately 2% to 3% of births with a variable frequency in different populations.[9] Congenital malformations or birth defects may be detected soon after birth or later, depending upon the nature of the defect. Congenital malformations are significantly contributing to infant mortality and morbidity; high-income nations have devised precise observation frameworks to discover the prevalence of CAs for the development of effective preventive systems.[10]

The frequency of CAs in our own hospital deliveries (2.91%, 29.19/1000 total births) is much higher compared to other local hospitals. For example, a study done in Kohat reported a frequency of 9.7/1000 live births,[11] and another study in Karachi demonstrated a frequency of 11.4/1000 live births.[12] Data from a hospital-based study in India reported a frequency of congenital anomalies at 1.91%.[13] Interestingly, our data corresponds to findings in Iran that report a frequency of congenital anomalies at 29.4/1000 live births.[14] This is also similar to a study done in Canada (36.18/1000).[15]

In our study, the CAs related to the central nervous system (CNS) were the most common (58.06%). CNS anomalies included meningomyelocoele, anencephaly, and hydrocephalus, among others. Some cases of hydrocephalus were found in patients with spina bifida in our study. These findings favor the results of a Turkish study showing CNS related anomalies as the commonest CA.[16] CNS anomalies are considered the most common in live born and still born fetuses in Egypt and in other countries as well.[17]

Congenital heart defects (CHD), however, could not be documented in our study because children born with heart defects were transferred to the Lady Reading Hospital (LRH) Peadiatric Cardiology unit. In the future, we would like to do a study that includes congenital heart defects (CHD) to determine this frequency and other associated anomalies.

In this study, males were more commonly affected than females (1.2:1). Congenital malformations that exist more commonly in males have also been reported in other studies.[17] Lisi reported that sex distribution varied significantly and that it depends on the type of malformation and whether it is isolated, associated with another malformation, or syndromic.[18] As a result, sex distribution should be studied in every CA separately and not in the group of CAs as a whole.

Inter-cousin marriages are very common in countries with different religious and ethnic backgrounds.[19] Pakistan has been noted to have the world's highest prevalence (61%) of consanguineous marriages between first and second cousins.[20]

In our study, consanguinity was present in 67.7% of cases with various CAs. A study performed in Iran demonstrated that CAs were 3.5 times more common in consanguineous marriages as compared to non-consanguineous marriages.[21]

Furthermore, only 32.3% of the mothers had received folic acid or multivitamins. This may represent a lack of adherence to these dietary recommendations to avoid CAs. To reduce the occurrence of neural tube defects, it is recommended for all pregnant women to consume 400 mg of folic acid daily.[22]

It has been suggested that the increasing age of mothers is associated with an increase in chromosomal meiotic errors and is probably the only non-genetic risk factor for trisomy in human beings.[23] Mean maternal age in our study was 30±8 years with only 19.4% of mothers above 40 years of age. Our results are similar to a study done in Iran (maternal age 25.69+5.54 years, 8.7% >35 years age).[19] Besides maternal age, multiparity and multigravidas are also associated with an increased prevalence of CAs.[24] Almost 70% of mothers in our study were multigravida, which is consistent with a study by Qazi that showed 2 out of 3 congenital malformations in newborns were associated with maternal multigravida.[25] This is in contrast to a study by Perveen that demonstrated more CAs in primigravida mothers.[16] Maternal age is an important parameter affecting the birth of a fetus with congenital malformations. For this reason, females who are older than 30 years of age need to be examined more carefully since the risk of giving birth to a fetus with congenital malformations is greater.

In our study, 77.6% of babies with CAs were found to have birth weights of <2.5 kg. A high frequency of birth defects was also reported in other studies that examined infants with low or very low birth weight, including premature infants.

Our findings are consistent with another local study showing that 43.5% infants birth weight of <2.5 kg have congenital anomalies.[28] Intrauterine growth restriction (IUGR) could be a primary predisposing factor for these anomalies or may occur secondarily as a result of existing CAs. It may even be that both IUGR and CAs may coexist with some common etiologic factors.[26]

No active smoking was present in our study; however, passive (second-hand) smoking during pregnancy was present in 16.1% cases. This is now an established fact that the risk of congenital malformation is significantly increased by passive second-hand smoke exposure during pregnancy.[27] Other risk factors like teratogenic drug use were not that frequently discovered in our study.

One of the limitations of this study is that there is a well-known association between folic acid deficiency and neural tube defects. Serum and blood folate levels could not be determined due to their high cost. As a result, the definitive diagnosis of chromosomal abnormalities could not be made because of the lack of availability of these appropriate tests. Since this study was a cross-sectional descriptive study, the findings may not be projected to the entire population. Nevertheless, these results emphasize an important public health issue and present a baseline for other well-designed studies.

Congenital anomalies are important causes of fetal deaths; thus, it becomes mandatory to determine the incidence and prevalence of congenital abnormalities in society. The present study demonstrated a high frequency of congenital malformations in the young age group and especially among primigravida women. The most frequently reported risk factor was consanguineous marriage. CNS malformations were the most prevalent anomaly detected. Early prenatal diagnosis is therefore very helpful in decreasing perinatal mortality by allowing for the option of early termination of pregnancy. This study contributes the frequency of congenital anomalies and the self-reported risk factors of congenital anomalies in a tertiary referral center in Pakistan. Further studies are required to evaluate interventions that may be oriented to eliminate risk factors and reduce the incidence of congenital anomalies.

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Acknowledgments

Dr Iftikhar Qayum, Research Department, Rehman Medical College, Peshawar, Dr Rashid Iqbal and Dr Ali Raza, Community Health Science Department, Rehman Medical College, Peshawar, Pakistan, and doctors and staff of Obstetrics & Gynaecologiy Department, Khyber Teaching Hospital, Peshawar, Pakistan are acknowledged for their support and advice.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conception and design the work/idea: AK. Collect data/obtaining results, Analysis and interpretation of data: AK, MZ, FA, MF, ArK, JZ, HU, RU, SB. Write the manuscript: AK, MZ. Critical revision of the manuscript: AK. Approval of the final version: AK, MZ. Contribution of patients or study material, Obtaining financing: AK. Statistical advice: AK, MZ.

Cite as:

Khan A, Zuhaid M, Fayaz M, Ali F, Khan A, Ullah R, et al. Frequency of Congenital Anomalies in Newborns and Its Relation to Maternal Health in a Tertiary Care Hospital in Peshawar, Pakistan. Int J Med Students. 2014 Nov-2015 Mar;3(1):19-23.

IJMS International Journal of Medical Students

Original Article

Exposure and Knowledge of Sharps Injuries among Medical Students in Seven States of Mexico

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Abstract

Background: Medical students are vulnerable to accidental exposure to blood-borne pathogens when performing clinical activities. Knowledge of both the prevalence of exposure and necessary reporting procedures is important to minimize the risk of harm to medical students. **Methods:** A cross-sectional online survey of medical students from 19 universities from seven states in Mexico was utilized to determine the prevalence of needle stick injuries amongst medical students and the associated reporting procedures. **Results:** We included 312 respondents; of these, 52.24% were men and 47.76% were women, and the mean age was 23.19 years (SD ± 2.11 years). Nearly all of them (94.23%) were medical students doing clerkships in public hospitals. Mean knowledge score of blood-borne pathogens was 3.6 (SD ± 1.16) on a scale of 0-10 designed specifically for this study. Thirty-five per cent of the respondents had sustained a needle stick injury at some point during their medical school training, and 33.97% reported some type of mucocutaneous exposure. Overall, the non-reporting rate of needle stick injury was 48.34%. Approximately 25% of the respondents were not familiar with reporting procedures in the event of a needle stick injury or mucocutaneous exposure; 61.50% had received information from their hospital about the standard protocol to follow after a blood or body fluid exposure. **Conclusion:** In this Mexican population of medical students, there is a high risk of suffering needle stick injuries during medical training. Furthermore, knowledge regarding prevention, evaluation, and reporting of needle stick injuries is suboptimal.

Keywords: Needle Stick Injury, Medical Student, Body Fluids, Blood-Borne Pathogens, HBV-AS04 vaccine, HIV, Preventive Measures (Source: MeSH-NLM).

Introduction

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Sharps injuries are frequent events among medical students.[1] As many as one out of three exposed medical students may be at risk of acquiring human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection during medical training due to blood or body fluid exposures, with the intern year of training being the most common period in medical training to endure a needle stick injury (NSI) or mucocutaneous exposure.[2] Under-reporting is common because of the belief that most exposures are not significant, time constraints, and not knowing where to report the event.[2-3] Furthermore, medical students are more likely to ignore the exposure than residents or fellows.[4]

The National Institute for Occupational Safety and Health (NIOSH) defines NSIs as "those caused by needles such as hypodermic needles, blood collection needles, intravenous (IV) stylets, and needles used to connect IV delivery systems". (Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/niosh/, updated 2015 February 15; cited 2015 February 26.) The risk of NSIs among health care workers is high; this risk can best be reduced by taking proper preventive measures including immunization against HBV, eliminating unnecessary injections, implementing universal precautions, eliminating needle re-capping and disposing of the sharps into a sharps-container immediately after use. Furthermore, utilization of safer devices such as needles that sheath or retract after usage, provision and use of personal protective equipment, and training workers in the risks and prevention of transmission can all reduce the likelihood of NSIs. Post-exposure prophylaxis with antiretroviral medications has been shown to reduce the risk of HIV transmission by 80% (Centers for Disease Control and Prevention. Available from: http://www.cdc.gov/hicpac/2007IP/2007isolationPrecautions.html, updated 2010 December 9; cited 2015 February 26).[5]

Data regarding the psychological impact of a needle stick or sharps injury is limited when compared to published research describing the physical risk of seroconversion. Healthcare workers who have had a needle stick or sharps injury undergo high levels of anxiety and depression during work, and these are exacerbated after the injury.[6]

The aim of this study is to evaluate the prevalence of NSIs and mucocutaneous exposures, knowledge of blood-borne diseases, and post-exposure actions taken by interns and medical students from different medical schools in Mexico.

Methods

We performed a cross-sectional, anonymous, open online survey from April to July 2013 that included medical students from

Submission: Feb 18, 2015
Acceptance: Feb 25, 2015
Publication: Mar 24, 2015
Process: Peer-reviewed

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19 universities from 7 states in Mexico. A total of 400 questionnaires were sent; we included only fully and consistently answered questionnaires. Those questionnaires that had inconsistent answers with discrepancies were eliminated

The questionnaire consisted of two sections with 28 questions covering past experiences of NSIs, mucocutaneous exposures, the circumstances surrounding the injury, reporting protocols, the use of gloves, recapping practices, HBV vaccination, and the perceived level of anxiety after exposure and post-exposure prophylaxis. The respondents were also asked to select from a list of pathogens the ones they thought could be transmitted by blood or body fluid exposure. The list included HIV, HBV, HCV, cytomegalovirus, Epstein Barr Virus, dengue virus, Trypanosoma spp, Mycobacterium tuberculosis, Leishmania spp and Treponema pallidum. Streptococcus pneumoniae and Neisseria meningitidis were added as distracters. Five questions asked for basic demographic data.

Consent was presumed upon submission of the questionnaire. Data was obtained using a Google Survey (Google Incorporated, Mountain View, CA). The online web link was distributed using Facebook (www.facebook.com) and by personal e-mail. Once the questionnaire was constructed, it was randomly applied to a group of 15 medical students for the pre-evaluation of the understanding of the questions. Afterwards, simple modifications were made before applying the survey to the study group. All of the study questionnaires were sent and evaluated by the authors.

We calculated an approximate population of 350,000 students that could potentially be surveyed. Based on this population, we estimated that for a confidence level of 95%, a total of 400 questionnaires would be required. (www.surveysystem.com). All data was analyzed using simple descriptive statistics. The variables were expressed in mean, median and standard deviation. A Chi-squared test was used when comparing proportions and a Wilkinson sum test was used when comparing means. A p-value of ,0.05 was considered to be statistically significant. We used Statistical Package for the Social Science S.P.S.S. version 18 software.

The study was approved by the Ethics Committee on November 22th, 2013 under the approval code IF13-004.

Results

A total of 338 questionnaires were completed. Twenty-six were eliminated because they had inconsistent answers and discrepancies. We analyzed the data from the remaining 312 respondents. Of these, 52.24% were from men and 47.76% from women. Seventy-three per cent of the respondents (n=228) were from Nuevo Leon state, 9.94% (n=31) from Mexico City, 8.33% (n=26) from Baja California state, 5.45% (n=17) from Puebla state, and 2.56 (n=8) from Jalisco state, and 2 more from other states.

Two-hundred and eight questionnaires (66.9%) were from the Universidad Autónoma de Nuevo León, 26 (8.33%) from the Universidad Nacional Autónoma de México, 20 (6.41%) from the Universidad de Monterrey, 15 (4.81%) from the Universidad Xochicalco, 17 from the Universidad Autónoma de Puebla, 8 from the Universidad de Guadalajara, and 18 more from other universities.

A total of 294 students (94.23%) were doing their clerkships in a public hospital while 16 (5.13%) were assigned to a private hospital at the time of the survey.

The mean student age was 23.19 years (range 20–30 years) (SD +2.11 years). Two-hundred and ninety five (94.55%) respondents had had clinical practice in the hospital. Two-thirds (218/312) were final year students. Sixty-three percent (199/312) had attended at least one lecture about NSIs and mucocutaneous exposure during their medical education and 56.73% (177/312) reinforced their knowledge of sharps and mucocutaneous exposure with a lecture before starting their clinical practices.

Students were asked to rate their own knowledge about NSIs and mucocutaneous exposures as bad, poor, regular, good, or very good. Eleven (3.53%) students rated their knowledge as bad, 26 (8.33%) as poor, 128 (41.03%) as regular, 131 (41.99%) as good, and 16 (5.13%) as very good.

The percentages of students who correctly identified blood-borne pathogens were as follows: One hundred percent (n=312) of the students identified HIV as a blood-borne pathogen, 96.15% (n=300) identified HBV, 91.98% (n=287) identified HCV, 32.69% (n=102) identified cytomegalovirus, 21.47% (n=67) identified Epstein Barr virus, 9.61% (n=30) identified dengue virus, 7.69% (n=24) identified Trypanosoma spp, 21.79% (n=68) identified M. tuberculosis, 6.73% (n=21) identified Leishmania spp and 25.96% (n=81) identified T. pallidum as blood-borne pathogens. One point was added for each correct answer and one was subtracted for each incorrect answer (theoretically, there was a maximum score of 10 and a minimum of 0 points). In the current study, the mean score was 3.66 (range 3-10) (SD +1.16). When we compared results from students from public universities to private universities, there were no statistical differences (p=0.97).

Of the respondents, 68.0% from public universities and 51% from private universities stated that they had received information about prevention practices for related injuries during their medical training (p=0.005), demonstrating a significant difference between public and private universities. Thirty-four per cent (106/312) of the respondents had sustained an NSI at some point during their medical school training and 104 (33.33%) sustained some type of mucocutaneous exposure. Seventy-nine students (25.32%) had suffered an accident during the six months prior to answering the questionnaire. When comparing medical students who sustained NSIs, 26.9% belonged to public universities while 38.5% were from private universities (p=0.050). Almost 90% (277/312) of the respondents knew of at least one fellow student who had had a blood or body fluid exposure. Of the 218 students in their last year of medical studies, 37.15% (n=81) had sustained at least one NSI. ***Figure 1*** demonstrates the percent of medical students with NSIs according to their year of training.

The overall non-reporting rate of NSIs and mucocutaneous exposures was 48.34% (n=73). Of the students who reported the incident, 67.95% (n=53) did it during the first hour post-exposure. Only two of them (2.5%) reported the incident 48 hours after exposure (***Table 1***).

Blood tests for blood-borne pathogens including HIV, HBV and HCV were performed in both the source patient and the student who reported the accident in 76.92% and 58.97% of the events, respectively. Only 8 (10.25%) of the incidents involved a patient already diagnosed with an HIV, HBV, or HCV infection. The source patient could not be identified by the respondent in 6.41% (n=5) of cases. Post-exposure prophylaxis was administered in 25.64% (n=20) of the cases reported (***Table 1***).

Students reported, on a 1 to 10 scale, the degree of anxiety they felt after the accident using 1 to report no anxiety and 10 to report being very anxious. Twenty-six (17.21%) of the respondents reported 10 as their level of anxiety after the incident; 11 (7.28%) reported 1. The mean level of anxiety among the injured students was 6.06 (SD +2.90).

A total of 151 participants reported an NSI and/or a mucocutaneous exposure. Overall, the number of accidents reported was as follows: 67.54% (n=102) of the participants who suffered an accident had had 1 event, 27.81% (n=42) 2 to 3 events, and 4.63% (n=7) had experienced more than 3 events. Most of these accidents were not caused by or attributed to another health care worker (76.15%).

As for the safety precautions during the incidents, 83.44% (n=126) of the students were using gloves during the event. Re-capping used needles was reported as a typical maneuver by 74.68% (n=233). Only 39.07% (n=59) of the students were supervised while doing the procedure that caused the accident. Approximately a quarter (79/312) of the respondents were not familiar with reporting procedures in case of an NSI or a mucocutaneous exposure; only 61.5% had received information from their hospital about the standard protocol following a blood and body fluid exposure. Fifty nine percent (185/312) of the students would ask the resident on call for advice in case of an incident, 14.2% (45/312) would ask the attending physician, 4.49% (n=14) would ask a nurse, and 2.88% (n=9) would ask a fellow student. In this survey, only 39.7% (n=124) of the students participating had completed the 3 doses of HBV vaccination.

Discussion

In this study, 34% of the students surveyed had suffered an NSI; similarly, 33% had experienced a mucocutaneous exposure. Thirty-seven percent (81/218) of the students that were in their final year of medical school sustained at least one NSI during their medical studies. A previous study by Salzer and colleagues of medical students from the United Kingdom, Austria, and Germany reported an incidence of NSI in medical students in their final year of training at 34% and this was as high as 59% in the United States in graduate students. None of the mentioned studies, however, evaluated the number of procedures that the average medical student actually performs to assess the risk per procedure.[2-7] In a similar study of 455 medical students from the United States, Kessler and colleagues registered a non-reporting rate of 82.9%, which was considerably higher than the non-reporting rate of 48.34% in our study.[3]

A previous study conducted in the Hospital Universitario Dr. José Eleuterio González during a five year period (2005-2011) reported that 45.42% of occupational exposures in healthcare workers occurred in medical students. In the same study, 87.7% of exposures were percutaneous injuries and 12.3% mucocutaneous exposures.[8] In our study, medical students reported a similar number of NSIs (n=110) and mucocutaneous exposures (n=106), suggesting that mucocutaneous exposures are more likely to go unreported, a finding similar to that in a study by Kessler and colleagues in the United States where 82.9% of the mucocutaneous exposures were not reported.[3] We believe that the perception of a lower risk of acquiring a disease by mucocutaneous exposure than by NSIs is associated with lower reporting.

Figure 1. Blood and Body Fluid Exposures by Year in Medical Students.

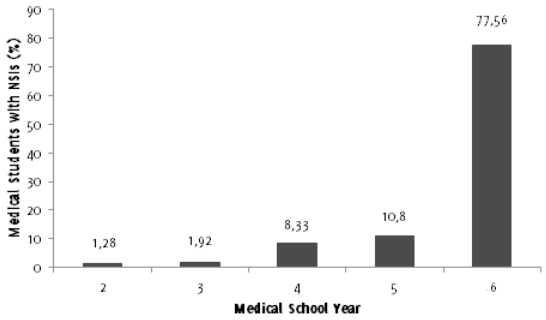

Table 1. Responses Provided by Medical Students on Reporting Procedures.

Characteristics	Frequency	%
Did you report this accident?		
Yes	78	51.66
No	73	48.34
Was the source patient identified?		
Yes	73	93.58
No	5	6.41
Was the source patient already diagnosed with a HIV, HBV or HCV infection?		
Yes	8	10.25
No	62	79.48
Unknown	8	10.25
Were serology tests performed on you after the accident?		
Yes	46	58.97
No	32	41.02
Were serology tests performed on the source patient?		
Yes	60	76.92
No	18	23.07
Did you receive post–exposure prophylaxis?		
Yes	20	25.64
No	58	74.35
In case of a blood or body fluid exposure, do you know where to report the incident in your hospital?		
Yes	233	74.68
No	79	25.32
In case of a blood or body fluid exposure, who's the first person you would ask for advice?		
Fellow student	9	2.88
Resident on call	185	59.29
Nurse	14	4.49
Attending physician	59	14.42

As shown by French and Pakistani studies, an increase in the level of practice of universal precautions reduces the incidence of NSIs.[9,10] Salzer and colleagues indicate that education regarding NSIs may reduce the risk significantly.[2] Although 63% (199/312) of the respondents attended at least one lecture about NSIs and mucocutaneous exposures, 74.68% reported recapping used needles as a usual maneuver, and 16% were not using gloves during the accident. This low compliance with universal precautions is probably due to the lack of continuous reminders and to human error.

Self-assessed knowledge of NSIs was rated as very good by only 5.1% of respondents. The results about knowledge of blood-borne pathogens was 100% for HIV and more than 90% for HBV and HCV; overall, however, the evaluation score of the population studied was low (average 3.6). This underscores the need for continuous reinforcement of safety and prevention measures during medical training and beyond.

Reporting of blood and body fluid exposures is critical because HBV immunoglobulin and vaccine should be administrated within the following days after a percutaneous exposure to HBsAg-positive blood, providing an estimated 85-95% protection from HBV infection. HIV prophylaxis should be started as soon as possible.[5,11] In our study, only 39.7% (124) of the students had completed the three doses of HBV vaccination. Compared to results shown by Fica and colleagues in Chilean students where 98% of the students who suffered a NSI were vaccinated against HBV, in our survey there was a higher rate of susceptibility to become infected with HBV after a blood or body fluid exposure.[11] In Mexico there is no law that obligates a healthcare worker to receive mandatory vaccination; thus, this in part explains the low compliance.

Self-reported level of anxiety was used to check the psychological impact of suffering a blood or body fluid exposure. This method could magnify the real level of anxiety among the students mainly because other variables such as personality and family stressors were not considered due the retrospective nature of the survey. Considering these limitations, a mean self-assessment of 6.1 on a scale of 1 to 10 is interesting because post-traumatic stress disorder in trainee doctors has been shown to be four times greater after an NSI.[13]

This survey studied a sample of students from different medical schools in Mexico. Although we cannot extrapolate our results to the whole Mexican medical student population, we consider our study to be a reflection of the general knowledge and need for improvement in education and prevention measures among Mexican medical students. The web link was distributed openly from person to person via e-mail and Facebook. This social network has been associated with a high daily usage among medical students (64%) where the majority of medical students that use this network believe that they are equally active on Facebook as in real life.[14] Thus we consider this method of distribution adequate for our survey.

We acknowledge our inability to calculate an accurate response (calculated to be 84.5%) rate because of the nature of our survey and the possibility for a third person distribution, but we believe that the number of questionnaires answered can give an important perspective of the general knowledge that Mexican medical students and interns have regarding NSIs.

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Acknowledgments
None.

Conflict of Interest Statement & Funding
The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea: ACO, XDR, MMP. Collect data/obtaining results: XDR, RHG, MMP, RVV, IDP. Analysis and interpretation of data, Write the manuscript: ACO, RHG. Critical revision of the manuscript: ACO, EGG. Approval of the final version: ACO.

Cite as:
Camacho-Ortiz A, Díaz-Rodríguez X, Hernández-García R, Martínez-Palomares M, Chávez-Moreno S, Garza-González E, et al. Exposure and Knowledge of Sharps Injuries by Medical Students in Seven States of Mexico. Int J Med Students. 2014 Nov-2015 Mar;3(1):24-8.

Health Literacy Levels among Outpatients at a Tertiary Hospital in Delhi, India

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Abstract

Background: Health literacy is defined as the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good health. This study was conducted to determine health literacy levels and the associated factors among patients attending the outpatient departments of a tertiary care hospital in Delhi. **Methods:** A hospital-based cross-sectional study was carried out in a tertiary care teaching hospital in Delhi over a period of four months. A total of 150 patients were included in the study. Fifty patients from the Diabetes Clinics, 50 patients from Hypertension Clinics, and 50 patients with anemia from the Antenatal Outpatient Department (OPD) were selected using a convenience sampling method. Data was analyzed using Epi Info software. Statistical analysis was conducted with the chi-square test and the Fisher's exact test. P values less than 0.05 were considered significant. **Results:** Out of 50 diabetic subjects, 37 (74%) understood the information about their blood sugar levels as explained to them by the doctor. Similar results were found among hypertensive subjects as well. Furthermore, education status was significantly associated with health literacy. In terms of understanding the regimen of medications, significant association was seen with age, sex, and education. **Conclusion:** Education status, age, and gender are important determinants of health literacy. Our results support that innovative strategies of communication should be used to improve health literacy among patients.

Keywords: Health Literacy, Knowledge, Outpatient Clinics, Diabetes Mellitus, Hypertension (Source: MeSH-NLM).

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Introduction

The World Health Organization (WHO) defines health literacy as cognitive and social skills that determine the motivation and ability of people to understand, gain access and use the information to obtain good health. By improving people's access to health information and their capacity to use it effectively, health literacy is critical to empowerment (WHO. Available from: http://www.who.int/healthpromotion/conferences/7gchp/track2/en/, cited 2015 Jan 02).

Health literacy includes an individual's ability to understand instructions and other health related documents. Examples include instructions written on drugs, appointment slips, information brochures, physicians' advice on drug schedules, counseling, compliance, and the ability to utilize and negotiate health-care systems.[1]

Among the different barriers to utilization of health care services like financial issues, lack of access to health providers and inadequate preventive care, low health literacy is one of the most important factors.[2] Improved health literacy develops competencies for the individual to assimilate, comprehend, and adapt to healthy practices and reduce risky behaviors.[3] Several studies have shown that low health literacy is associated with higher rates of mortality and lack of preventive behaviors such as screening tests.[4,5] These patients are more likely to indulge in high-risk behaviors. Low health literacy generally relates to poor physical and mental health.[6,7] Studies have shown that low health literacy, in terms of poor understanding of medical information, may lead to poor self-adherence to drugs and higher propensity to have non-communicable diseases risk factors (tobacco use, hospitalizations, and substance abuse).[8-11]

Keeping the above in mind, it is important to gain an understanding of health literacy rates among patients in India. It is important to study this topic because a number of factors play a role in health, health seeking behaviors, and compliance. This topic is especially relevant in an Indian context where cultural factors play a crucial role in both health and disease. An understanding of health literacy may help to plan future strategies to improve general health care. This study was conducted with an objective to determine health literacy rates and the associated factors among patients attending the outpatient clinics of a tertiary care hospital in Delhi.

Methods

A cross-sectional study was conducted in a tertiary care teaching hospital in Delhi over a period of four months. All patients attending Medicine and Obstetrics Outpatient Department (OPDs) in the hospital constituted the study population.

The sample size was calculated on the basis of findings of a previous study that assessed the mean score for health literacy in outpatient clinics in India.[3] Taking 95% confidence intervals and an alpha error of 5%, the sample size was calculated to be 102. However, a total of 150 patients were included in the study.

Submission: Feb 9, 2015
Acceptance: Mar 24, 2015
Publication: Mar 31, 2015
Process: Peer-reviewed

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Fifty patients in each of Diabetes and Hypertension clinics in the Department of Medicine and 50 patients with anemia from the Antenatal OPD in the Obstetrics Department were selected by a convenience sampling method. All adult patients aged 18 years or older who gave consent to participate in the study were included. Patients who were seriously ill, needed urgent medical attention and required admission were excluded.

The reason for choosing the conditions was the increasing trend of non-communicable diseases in urban areas in India. Anemia was chosen as the topic for antenatal patients since the prevalence of anemia is high in pregnancy in India. Anemia is also one of the important causes of maternal morbidity and mortality in India. Thus, an understanding of these diseases may be helpful for future policy decisions in public health in relation to health literacy.

A pretested, predesigned, semi-structured questionnaire consisting of eleven items on demographic characteristics like age, sex, educational status, and occupation was developed. Education status was broadly grouped into formal and informal education. Similarly, occupational status was divided into unemployed and employed. The health literacy among study subjects was assessed using the questionnaire and included the patients' level of understanding of their illness and the interpretation of the numeric values related to their illness as told to them by the health care provider and as indicated by various investigations.

The questionnaire was pilot tested in a different setting among patients for assessing its feasibility and reliability. Suitable modifications were done afterwards. Cronbach's alpha, which is a coefficient of internal consistency, was calculated to be 0.82. Experts in relevant fields were also asked about their opinion during the development of the questionnaire. The documents related to the investigations, diagnosis, and prescription of medications were also examined by the researcher to validate the accuracy of information provided by study subjects such as the dose of medications being taken and the value of hemoglobin. The subjects were interviewed, maintaining privacy by the researcher, in their local language, and it took 10-12 minutes to complete each interview.

Data collected was analyzed using Epi-Info software. The results were presented in mean ± standard deviation (SD) and proportions wherever relevant. Any difference between two proportions was assessed by a chi-square test for normal distributions and the Fisher exact test for non-normal distributions of data. P-values less than 0.05 were considered significant. Patient data confidentiality was maintained throughout the study. Written informed consent was obtained from all participants. Institutional ethical clearance was also obtained.

Results

Socio-Demographic Characteristics

Out of 50 subjects who were diabetic, 41 (82%) were more than 45 years of age. Out of the 50 subjects who were hypertensive, 18 (36%) were above the age of 60 years, while among 50 female subjects from the antenatal clinic, 45 (90%) were in the age group of 15 to 30 years old. Among the diabetic subjects, 32 (64%) were males and 18 (36%) were females. Among hypertensive subjects, 28 (56%) were males and 22 (44%) were females. Small percentages of diabetics (10%) and hypertensive patients (14%) and about one-third of obstetric OPD patients (30%) reported that they had not received any formal education. Out of 50 diabetic subjects, 7 (14%) were unemployed. Among the 50 hypertensive subjects, 10 (20%) were unemployed while 35 (70%) of the anemic subjects were unemployed (***Table 1***).

Health Literacy among Diabetic Subjects

Out of the 50 diabetic subjects, 74% understood the significance of the information about their blood sugar level as explained by the doctor. For example, patients were asked details such as what the normal range of blood sugar levels is and what was the target for blood sugar levels set for them by their doctor for optimum control. Twenty-six percent of participants did not understand the same. However, no significant difference was found between various age groups (p=0.21). Similarly, no association was seen with occupation status and gender (p >0.05). There was a difference in those who did not receive any formal education (20.0%) and those who had received formal education (80.0%) in terms of their understanding of the information given to them by their healthcare provider. This difference was statistically significant (p=0.01), as shown in ***Table 2***.

Table 1. Socio-Demographic Characteristics of Study Subjects.

Characteristic	Diabetes Mellitus OPD* n=50 [freq(%)]	Hypertension OPD n=50 [freq(%)]	Obstetrics OPD n=50 [freq(%)]	Total N=150 [freq(%)]
Gender				
Male	32 (64)	28 (56)	0 (0)	60 (40)
Female	18 (36)	22 (44)	50 (100)	90 (60)
Age (in years)				
Less than 45	9 (18)	16 (32)	45 (90)	70 (46.7)
More than 45	41 (82)	34 (68)	5 (10)	80 (53.3)
Education status				
No formal education	5 (10)	7 (14)	15 (30)	27 (18)
Formal education	45 (90)	43 (86)	35 (70)	123 (82)
Occupation				
Unemployed	7 (14)	10 (20)	35 (70)	52 (34.7)
Employed	43 (86)	40 (80)	15 (30)	98 (45.3)

Legend: * OPD - Outpatient Department.

Table 2. Associates of Health Literacy in Diabetes and Hypertension Outpatient Department.

Characteristic	Understood information			
	Diabetes OPD* n=37 **[freq(%)]**	P value	Hypertension OPD n=38 **[freq(%)]**	P value
Gender				
Male	23 (62.2)	0.74†	19 (50)	0.12
Female	14 (37.8)		19 (50)	
Age (in years)				
Less than 45	5 (13.5)	0.21†	11 (28.9)	0.48†
More than 45	32 (86.5)		27 (71.1)	
Education status				
No formal education	1 (2.7)	0.01†	0 (0)	0.01†
Formal education	36 (97.3)		38 (100)	
Occupation				
Unemployed	5 (13.5)	1.00†	6 (15.8)	0.22†
Employed	32 (86.5)		32 (84.2)	

Legend: * OPD - Outpatient Department. † Fisher exact test was used.

Questions were asked about the patient's understanding of the regimen of taking anti-diabetic medications. Eighty-four percent of the subjects reported that they understood the regimen as explained to them by the doctor. Among subjects less than 45 years, 44.4% said that they understood the regimen as told to them but this figure was 92.7% among subjects aged more than 45 years (p=0.01). Among subjects with no formal education, not a single subject understood this information, while among those with formal education, 93.3% were able to comprehend the information (p=0.01). Similarly, among occupational classes, only 11.9% of those patients who were unemployed understood the regimen; 88.1% of those who were employed understood the regimen. This was not statistically significant (p=0.31). A significantly higher proportion of females (100%) than males (75%) understood the information about their regimen (p=0.03).

Health Literacy among Hypertensive Subjects

Among subjects from the Hypertension Clinic, none among those with no formal education understood information about the blood pressure (i.e. normal values of blood pressure) and their target blood pressure levels as told to them by their doctor. Among those who had received formal education, 88.4% understood this information. This difference with respect to education status was statistically significant (p=0.01). A lower proportion of unemployed subjects understood the same information as compared to employed. This was not statistically significant (p=0.22). No difference was seen between gender and age groups (***Table 2***).

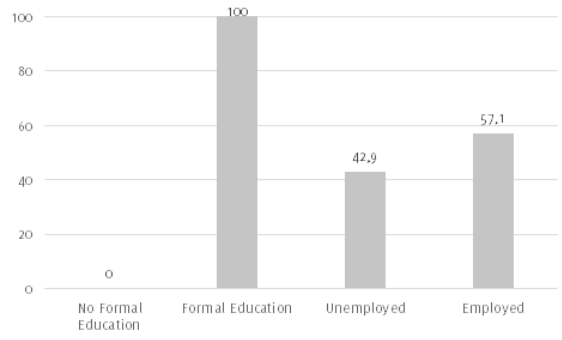
About 60% of study subjects reported that they understood the regimen of taking antihypertensive medications, including dosage, frequency, and side effects, as explained to them by their doctor. Among subjects less than 45 years old, 18.8% said they understood the regimen. This figure, however, was 79.4% among subjects aged more than 45 years old and represented a significant difference (p=0.01). Among those with no formal education, not even a single subject understood the information whereas among other groups with formal education training, 66.7% were able to understand the regimen (p=0.01). There was no significant difference seen in occupation. A significantly higher proportion of females (100%) than males (28.6%) understood the regimen (p=0.01).

Health Literacy among Anemic Subjects

In anemic subjects in obstetrics OPD, significant differences were observed between those educated formally and those who were not in terms of the understanding of the value of hemoglobin (p=0.01). Among occupational classes, 57.1% of those who were employed were able to understand the level of hemoglobin while 42.9% of those who were unemployed understood the same (p=0.34) (***Figure 1***).

Seventy percent of the subjects reported that they understood the regimen of taking drugs given to them for the treatment of anemia as explained by their doctor. Among subjects who received formal education, 73.3% understood the information about the regimen whereas among those who had not received formal education, 68.6% were able to understand the same. This difference was not statistically significant (p=0.73). There was no significant difference between occupation status.

Figure 1. Associates of Health Literacy in Antenatal Obstetrics Outpatient Departments.



Legend: Fisher exact test was used; P value <0.05 for education status.

Discussion

The present study demonstrated that health literacy varies among education classes where those with formal education have health literacy rates higher than other groups. Furthermore, these same individuals had better understanding of their illnesses. Similar findings were mentioned by Howard DH, et al., in 2006 where having a high school degree was significantly associated with health literacy and higher likelihood of good self-reported health.[12] However, significant differences were seen in certain age groups, genders, occupational classes, and with education in terms of patients understanding the regimen of medications explained to them by their doctor. This is an important aspect because it has been shown that the clarity of doctor's explanations was associated with patient understanding of care and self-efficacy.[13] Moreover, poor health literacy is found to be associated with worse glycemic control and a higher risk of complications.[14]

Among patients with hypertension, significant differences were present depending on the education status of subjects. Similarly, unemployed patients also had lesser understanding of the information provided by clinicians. These results are similar to those reported by Levinthal BR, et al., among hypertensive patients where health literacy was associated with education status.[15] Similarly, in diabetic patients, significant differences were seen among age groups, education classes, and occupation statuses in terms of the understanding of the regimen related to taking medications. Significantly more females than males reported to have understood the regimen. This is different from findings observed by Javadzade SM, et al., in their study conducted in Iran where subjects with low health literacy tend to be older, had fewer years of schooling, and were females. The reason for this discrepancy may be differences in the study population and socio-demographic characteristics in these two studies.[16] Another factor could be the number of visits to OPD, which can be confounded by gender.

For patients with anemia, significant differences were seen with education status. This is an important aspect when looking at the burden of anemia in pregnancy in India and its consequences. Studies have shown that women with adequate health literacy have significant differences in initiation and frequency of antenatal care, neonatal birth weight, maternal hematocrit, ferrous and folic acid tablet consumption, pregnancy weight gain, gestational age at birth, method of delivery, and duration of breastfeeding.[17] Low health literacy has its implications on patients' understanding of health messages and limits their ability to care for their medical problems.[18] It is also an independent risk factor for hospital admission and it is associated with higher morbidity and more healthcare utilization.[19,20]

This study provides the first insight into health literacy and its determinants in an Indian setting. It suggests important policy implications for the future in terms of the training of health professionals in communication skills. Non-random sampling is one of the limitations of this study, but important points of concern are well understood.

India is a country with a huge population burden. The country has challenges of tackling the dual burden of communicable and non-communicable diseases. As per Global Status Report on non-communicable diseases (NCDs) by WHO for the year 2014, the figures for India for premature NCD mortality rate and number of deaths due to NCDs are higher than other countries (WHO. Available from: http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf, cited 2015 Jan 02). Such scenarios do not present a promising picture for the future. Health literacy is now believed to be an important determinant of health, one that intersects with other determinants in a myriad of ways. Although health literacy is not the only pathway to better health outcomes, it is certainly an important avenue. Therefore, any effort to improve health outcomes should take into account the health literacy of the patient. For effective disease management and maintenance of health, one must be able to understand, interpret, and act on health information, whether it is communicated verbally or in written form.[21] Health literacy is certainly going to impact the health status of the country with its crucial role in prevention and control of diseases. Association of health literacy with education is an important finding for advocacy to improve the educational status of the country.

It can be concluded from this study that education status, age, and gender are all important associates of health literacy. Healthcare providers should be aware of these factors when dealing with patients in their OPD for effective communication. Furthermore, innovative strategies should be used to improve the levels of health literacy among patients.

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Acknowledgments
This project was completed as a part of short term studentship by the first author from the Indian Council of Medical Research (ICMR). The support is greatly acknowledged by the authors.

Conflict of Interest Statement & Funding
The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea: MS, JK. Collect data/obtaining results: MS. Analysis and interpretation of data: MS, JK. Write the manuscript: MS, CK. Critical revision of the manuscript: CK, JK. Approval of the final version: MS, CK. Contribution of patients or study material, Statistical advice: CK. Administrative or technical advice: JK.

Cite as:
Sahoo M, Kohli C, Kishore J. Health Literacy Levels among Outpatients at a Tertiary Hospital in Delhi, India. Int J Med Students. 2014 Nov-2015 Mar;3(1):29-33.

IJMS International Journal of Medical Students

Original Article

Antimicrobial Sensitivity Pattern of Microorganisms Isolated from Vaginal Infections at a Tertiary Hospital in Bangalore, India

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Abstract

Background: The vagina contains dozens of microbiological species in variable quantities and is, therefore, considered a complex environment. Among the microorganisms, bacteria have important repercussions on women's health. The present study was conducted to elucidate this type of vaginal isolates and their sensitivity towards currently used antibiotics. **Methods:** This was a retrospective study conducted at the Department of Obstetrics and Gynaecology, Sapthagiri Hospital, Bangalore, India from January 2012 to December 2013. All symptomatic women who had a high vaginal swab taken for culture and sensitivity testing were included in this study. Antibiotic susceptibility was tested using disc diffusion method (modified Kirby-Bauer's method). The antibiotic sensitivity patterns of isolated microorganisms were studied. **Results:** Out of 200 patients, 95% had positive vaginal cultures. Fifteen types of microorganisms were isolated. The highest frequency of infection was seen at the age of 20-30 years, followed by 41-50 years and 31-40 years, and a low frequency of infection was observed above 50 years of age. The most prevalent pathogen was *Escherichia coli*, followed by *Streptococcus agalactiae* and diphtheroids with equal incidence. Among the antibiotics tested, isolated pathogens were completely resistant to nalidixic acid and highly sensitive to meropenem and imepenem. **Conclusion:** The high prevalence of gynaecological infections demands that patients with symptoms undergo thorough investigation with cultures and sensitivity essays. Changes in treatment protocols are required to treat vaginal infections effectively.

Keywords: Vaginitis, Microbiota, Anti-Bacterial Agents, Microbial Sensitivity Tests (Source: MeSH-NLM).

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Introduction

The vagina is a complex ecosystem containing a variety of micro-organisms.[1] This unique environment undergoes significant changes throughout life, from birth to puberty and menopause.[2] Females are more prone to urinary and vaginal infections because of the anatomical and functional proximity to the anal canal and due to the short urethra.[3] The sex steroid hormones play a vital role in stabilizing this environment. In normal women, the estrogen accounts for the maturation of vaginal epithelium, resulting in the accumulation of glycogen which helps in the maintenance of vaginal pH.[4]

The causative organisms can be endogenous, iatrogenic or sexually transmitted. The human body harbours hundreds of organisms of gram-positive and gram-negative varieties in the lower one-third of vagina. A key protective role is played by the lactic acid-producing bacteria in keeping the vaginal pH low.[5]

Common organisms are *Neisseria gonorrhoea*, *Trichomonas vaginalis*, *Streptococcus agalactiae* (group B Streptococcus) and *Chlamydia trachomatis*. Presentation includes itching and pain in the external genitalia and vagina, painful sexual intercourse, and the presence of abnormal vaginal discharge.[6]

The balanced vaginal environment varies with practices like douching, dressing, use of contraceptives and sexual activity.[7] Coexistent factors like diabetes and pregnancy also play a role in the vaginal ecosystem imbalance. Surprisingly, not many studies have investigated the prevalence of vaginal infections in relation to age and that of the antibiotic sensitivity pattern.[8] Morbidity associated with these infections also affects the economic productivity and quality of life of many individual women and consequently of communities as a whole.

Many women believe that such infections are normal and part of the female experience and do not seek care due to shame or lack of information.[9] In the pregnant woman, these infections lead to preterm labour, chorioamnionitis, premature rupture of membranes and low birth weight of the neonate, leading to high perinatal mortality.[10]

These infections can be easily detected by simple tests such as a vaginal swab for culture and sensitivity testing, which inform us the causative organism as well the antibiotic to use against it.[11] As per the Centre for Disease Control and Prevention (CDC) guidelines, the management includes therapy based on susceptibility pattern, partner notification, follow-up and health promotion. The aim of our study was to identify the common organisms in vaginal infections and to discuss the sensitivity pattern based on culture sensitivity. By studying sensitivity pattern to antibiotics in these strains, we may revise the recommendations for treatment protocol in such patients.

Submission: Dec 18, 2014
Acceptance: Mar 31, 2015
Publication: Mar 31, 2015
Process: Peer-reviewed

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Methods

This is a retrospective study conducted at Department of Obstetrics and Gynaecology, Sapthagiri Hospital (a tertiary health care centre), Bangalore from January 2012 to December 2013. Two hundred women aged between 20 to 65 years who had presented with symptoms of vaginal infections were included based on the previous records of culture and sensitivity obtained from the Department of Microbiology. They were labelled with a unique identifier to ensure confidentiality and freedom from bias. All the women had presented with one or more of the following symptoms: vaginal discharge, dyspareunia, malodour, dysuria, itching and fever. Those using antibiotics during the last two weeks and those with a recent history of vaginal instrumentation were excluded from the study.

Three swabs were collected for each woman. The first sample was a high vaginal swab from which culture was performed using blood agar for gram-positive bacteria, MacConkey agar for gram-negative bacteria (especially the Enterobacteriaceae), and Sabouraud's dextrose agar for fungi. They were incubated for 48 hours. The second sample was used for direct microscopic examination of *Trichomonas vaginalis*. The cervical samples were collected in suspected cases only and processed for the detection of *Chlamydia trachomatis*. Once the samples were obtained, they were transported to the Microbiology Laboratory Department at Sapthagiri Hospital, Bangalore.

Identification of microorganisms: isolated bacteria were identified using conventional methods, including colonial morphology, Gram stain, motility, germ tube test and biochemical tests (DNAse, catalase, Indole, coagulase, lactose fermentation, urease, oxidase, sugar fermentation, citrate utilization). Identification of *Streptococci* was based on haemolysis and thereby categorized according to Lancefield's grouping.

Antibiotic susceptibility was tested using disc diffusion method (modified Kirby-Bauer's method). Antimicrobials tested for sensitivity were amikacin, ampicillin, amoxicillin, imepenem, meropenem, ceftazidime, ceftriaxone, tigecycline, ciprofloxacin, cefpodoxime, nalidixic acid and cefixime.

Data obtained were presented as distribution of microorganisms with respect to age, number and percentage of patients from which the microorganisms were isolated, and antimicrobial sensitivity patterns. Analysis was done using Microsoft Excel program. However, the analysis was done with respect to age only, as details of social factors were not available. Based on data obtained, observations were drawn regarding the age-specific infective rates and present status of antimicrobial sensitivity patterns.

The ethical approval for this study was given by the Ethics and Research Committee of Sapthagiri Institute of Medical Sciences and Research Centre, Bangalore.

Results

Out of 200 women enrolled in the study, 95% had positive vaginal cultures. Fifteen microorganisms, including gram-negative bacteria, were isolated. The highest infection rate was observed among women aged between 20 and 30 years (39.5%), followed by those aged 31-40 years (19.0%) and 41-50 years (31.0%), and the lowest frequency of infection was observed among those aged between 51 and 65 years (5.5%), as shown in ***Table 1***.

Table 1. Distribution of Microorganisms with Respect to Age and Infection Rates.

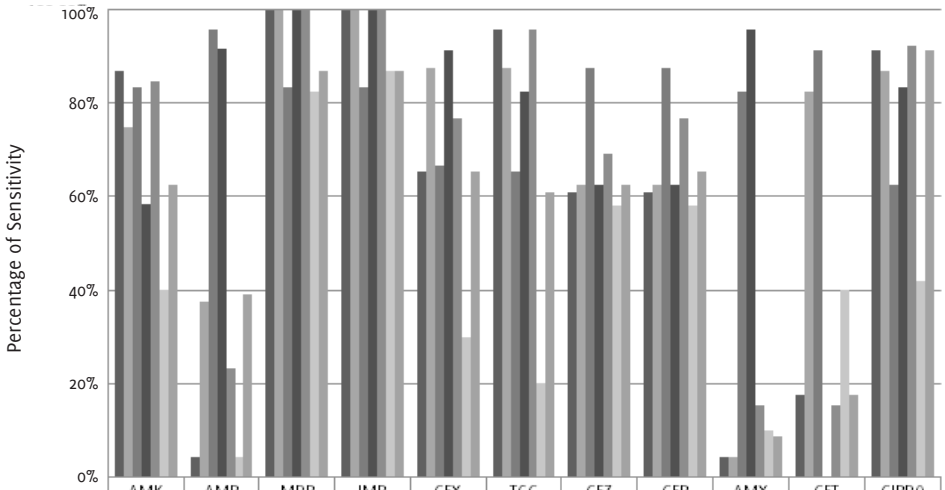
Age (years)	Frequency (%)	Organisms
20-30	79 (39.5%)	*Commensals*, other gram-negative bacteria, *extended-spectrum beta-lactamase-producing Escherichia coli, coagulase-negative Staphylococcus aureus, diphtheroids, Candida albicans, Acinetobacter.*
31-40	38 (19.0%)	*Commensals, Escherichia coli, Streptococcus agalactiae, Gardnerella vaginalis, Klebsiella pneumoniae, Citrobacter.*
41-50	62 (31.0%)	*Proteus vulgaris, Escherichia coli, Klebsiella pneumoniae, commensals, Micrococci, methicillin-resistant Staphylococcus aureus.*
>50	11 (5.5%)	*Escherichia coli, Enterococci, Klebsiella pneumoniae, commensals, Pseudomonas aeruginosa, Proteus vulgaris, coagulase-negative Staphylococcus aureus.*

Table 2. Types and Proportions of Microorganisms Recovered from Women with Vaginal Infections at Department of Obstetrics and Gynaecology, Sapthagiri Hospital, Bangalore.

Organism	Frequency (%)
Escherichia coli	**23 (11.5%)**
Extended-spectrum beta-lactamase-producing Escherichia coli	13 (6.5%)
Streptococcus agalactiae	12 (6.0%)
Diphtheroids	12 (6.0%)
Pseudomonas aeruginosa	10 (5.0%)
Methicillin-resistant Staphylococcus aureus	10 (5.0%)
Gram-negative bacteria	10 (5.0%)
Gardnerella vaginalis	10 (5.0%)
Citrobacter	10 (5.0%)
Enterococci	8 (4.0%)
Proteus vulgaris	8 (4.0%)
Coagulase-negative Staphylococcus aureus	8 (4.0%)
Micrococci	7 (3.5%)
Klebsiella pneumoniae	7 (3.5%)
Acinetobacter	7 (3.5%)
Candida albicans	5 (2.5%)
Mixed growth	2 (1.0%)

Microorganism with the highest frequency of infection was *Escherichia coli* (11.5%), followed by extended-spectrum beta-lactamase-producing *Escherichia coli* (6.5%), *diphtheroids* (6.0%), *Streptococcus agalactiae* (6.0%), *Pseudomonas aeruginosa* (5.0%), *Gardnerella vaginalis* (5.0%), methicillin-resistant *Staphylococcus aureus* (MRSA) (5.0%), *Citrobacter* (5.0%), and other gram-negative bacteria (5.0%). *Candida albicans* was isolated in 2.5% of the cases. Other organisms, such as *Proteus vulgaris*, coagulase-negative *Staphylococcus aureus*, *Acinetobacter*, *Klebsiella pneumoniae*, Micrococci and Enterococci, were also isolated (***Table 2***).

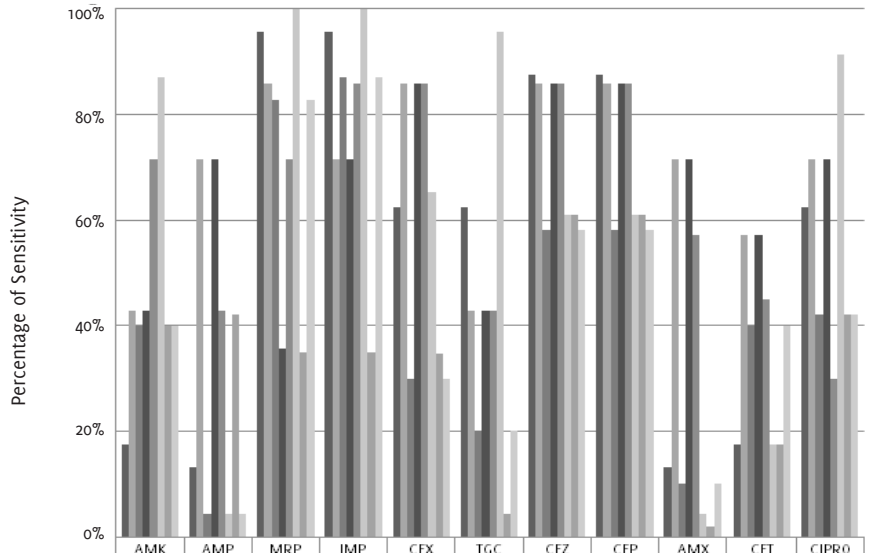
Figure 1. Antibiotic Sensitivity Pattern of the Isolated E. Coli, Proteus, Diphtheroids, Streptococci, Micrococci, Pseudomonas and Enterococci to 11 Antimicrobial Agents.



	AMK	AMP	MRP	IMP	CFX	TGC	CFZ	CFP	AMX	CFT	CIPRO
ECOLI	86,95%	4,35%	100%	100%	65,21%	95,65%	60,86%	60,86%	4,35%	17,40%	91,30%
PROTEUS	75%	37,50%	100%	100%	87,50%	87,50%	62,50%	62,50%	4,35%	82,60%	86,95%
DIPTHEROIDS	83,30%	95,65%	83,30%	83,30%	66,66%	65,21%	87,50%	87,50%	82,60%	91,30%	62,50%
STREPTOCOCCI	58,33%	91,66%	100%	100%	91,30%	82,60%	62,50%	62,50%	95,65%	0%	83,30%
MICROCOCCI	84,61%	23,07%	100%	100%	76,92%	95,65%	69,23%	76,92%	15,38%	15,39%	92,30%
PSEUDOMONAS	40%	4,35%	82,60%	86,95%	30%	20%	58%	58%	10%	40%	42%
ENTEROCOCCI	62,50%	39,14%	86,95%	86,95%	65,21%	60,86%	62,50%	65,21%	8,70%	17,40%	91,30%

Legend: ECOLI-Escherichia coli. Antibiotics: AMK-Amikacin, AMP-Ampicillin, MRP-Meropenem, IMP-Imipenem, CFX-Cefixime, TGC-Tigecycline, CFZ-Ceftazidime, CFP-Cefpodoxime, AMX-Amoxicillin, NA-Nalidixic acid, CFT-Ceftriaxone, CIPRO-Ciprofloxacin.

Figure 2. Antibiotic Sensitivity Pattern of the Isolated Coagulase-Negative Staphylococcus Aureus, Acinetobacter, Citrobacter, Klebsiella, ESBL-producing E. Coli, Gardnerella Vaginalis, MRSA and other GNB to 11 Antimicrobial Agents.



	AMK	AMP	MRP	IMP	CFX	TGC	CFZ	CFP	AMX	CFT	CIPRO
CONS	17,40%	13,05%	95,65%	95,65%	62,50%	62,50%	87,50%	87,50%	13,05%	17,40%	62,50%
ACINETOBACTER	42,85%	71,42%	85,71%	71,42%	85,71%	42,85%	85,71%	85,71%	71,42%	57,14%	71,42%
CITROBACTER	40%	4,35%	82,60%	86,95%	30%	20%	58%	58%	10%	40%	42%
KLEBSIELLA	42,85%	71,42%	35,71%	71,42%	85,71%	42,85%	85,71%	85,71%	71,42%	57,14%	71,42%
ESBL E.COLI	71,42%	42,85%	71,42%	85,71%	85,71%	42,86%	85,71%	85,71%	57,14%	45%	30%
GARDNERELLA VAGINALIS	86,95%	4,35%	100%	100%	65,21%	95,65%	60,86%	60,86%	4,35%	17,40%	91,30%
MRSA	40%	42%	35%	35%	34,79%	4,35%	60,86%	60,86%	2%	17,40%	42%
Other GNB	40%	4,35%	82,60%	86,95%	30%	20%	58%	58%	10%	40%	42%

Legend: CONS-Coagulase-negative *Staphylococcus aureus*, ESBL E.COLI-Extended-spectrum beta-lactamases-producing *Escherichia coli*, MRSA-Methicillin-resistant *Staphylococcus aureus*, GNB-Gram-negative bacteria. Antibiotics: AMK-Amikacin, AMP-Ampicillin, MRP-Meropenem, IMP-Imipenem, CFX-Cefixime, TGC-Tigecycline, CFZ-Ceftazidime, CFP-Cefpodoxime, AMX-Amoxicillin, NA-Nalidixic acid, CFT-Ceftriaxone, CIPRO-Ciprofloxacin.

Table 3. Antimicrobial Sensitivity Pattern of Isolated Microorganims.

Antiobiotic	Microorganisms						
	Escherichia coli	*Proteus vulgaris*	*Diphtheroids*	*Streptococcus agalactiae*	Micrococci	*Pseudomonas*	Enterococci
AMK	+++++	++++	+++++	+++	++++	+++	++++
AMP	+	++	+++++	+++++	++	+	++
MRP	+++++	+++++	+++++	+++++	++++	+++++	+++++
IMP	+++++	+++++	+++++	+++++	++++	+++++	+++++
CFX	++++	+++++	++++	+++++	++++	++	++++
TGC	+++++	+++++	++++	+++++	+++++	+	++++
CFZ	++++	++++	+++++	++++	++++	+++	++++
CFP	++++	++++	+++++	++++	++++	+++	++++
AMX	+	+	+++++	+++++	+	+	+
NA	+	+	+	+	+	+	+
CFT	+	+++++	+++++	+	+	++	+
CIPRO	+++++	+++++	+++++	+++++	+++++	+++	+++++

Legend: Legend: Sensitivity rates: 80%-100%: +++++, 60%-80%: ++++, 40%-60%: +++, 20%-40%: ++, 0%-20%: +. Antibiotics: AMK-Amikacin, AMP-Ampicillin, MRP-Meropenem, IMP-Imipenem, CFX-Cefixime, TGC-Tigecycline, CFZ-Ceftazidime, CFP-Cefpodoxime, AMX-Amoxicillin, NA-Nalidixic acid, CFT-Ceftriaxone, CIPRO-Ciprofloxacin.

Table 4. Antimicrobial Sensitivity Pattern of Isolated Microorganims.

Antiobiotic†	Microorganisms‡							
	CoNS	*Acinetobacter*	*Citrobacter*	*Klebsiella*	*ESBL-producing E. coli*	*Gardnerella vaginalis*	MRSA	GNB
AMK	+	+++	+++	+++	++++	+++++	+++	+++
AMP	+	++++	+	++++	+++	+	+++	+
MRP	+++++	+++++	+++++	++	++++	+++++	++	+++++
IMP	+++++	++++	+++++	++++	+++++	+++++	++	+++++
CFX	++++	+++++	++	+++++	+++++	++++	++	++
TGC	++++	+++	+	+++	+++	+++++	+	+
CFZ	+++++	+++++	+++	+++++	+++++	++++	++++	+++
CFP	+++++	+++++	+++	+++++	+++++	++++	++++	+++
AMX	+	++++	+	++++	+++	+	+	+
NA	+	+	+	+	+	+	+	+
CFT	+	+++	+++	+++	+++	+	+	+++
CIPRO	++++	++++	+++	++++	++	+++++	+++	+++

Legend: Legend: Sensitivity rates: 80%-100%: +++++, 60%-80%: ++++, 40%-60%: +++, 20%-40%: ++, 0%-20%: +. † AMK-Amikacin, AMP-Ampicillin, MRP-Meropenem, IMP-Imipenem, CFX-Cefixime, TGC-Tigecycline, CFZ-Ceftazidime, CFP-Cefpodoxime, AMX-Amoxicillin, NA-Nalidixic acid, CFT-Ceftriaxone, CIPRO-Ciprofloxacin. ‡ CoNS-Coagulase-negative Staphylococci, ESBL-Extended-spectrum beta-lactamase, MRSA-Methicillin-resistant *Staphylococcus aureus*, GNB-Gram-negative bacilli.

Escherichia coli (***Figure 1*** and ***Table 3***) was most sensitive to meropenem (100%) and imipenem (100%) and most resistant to amoxicillin (4.4%). Proteus vulgaris showed sensitivity to meropenem (100%), imipenem (100%), cefixime (87.5%), tigecycline (87.5%) and ciprofloxacin (87.0%). Diphtheroids showed sensitivity to ampicillin (95.7%), ceftriaxone (91.3%), cefpodoxime (87.5%), ceftazidime (87.5%), and others. *Streptococcus agalactiae* showed sensitivity to meropenem (100%), imipenem (100%), amoxicillin (95.7%), ampicillin (91.7%) and cefixime (91.3%). Micrococci showed 100% sensitivity to meropenem and imipenem. *Pseudomonas aeruginosa* and Enterococci were sensitive to meropenem and imipenem, as shown in ***Figure 1*** and ***Table 3***. Complete resistance to nalidixic acid was noted with all organisms.

As shown in ***Figure 2*** and ***Table 4***, coagulase-negative *Staphylococcus aureus* showed sensitivity to meropenem (95.7%), imipenem (95.7%), cefpodoxime (87.5%), ceftazidime (87.5%), cefixime (62.5%) and tigecycline (62.5%). Acinetobacter showed 85.7% sensitivity to meropenem, cefixime and cefpodoxime; Citrobacter and other gram-negative bacteria showed sensitivity to imipenem (87.0%) and meropenem (82.6%). *Klebsiella pneumoniae* showed sensitivity to ceftazidime and cefpodoxime. Extended-spectrum beta-lactamase-producing *Escherichia coli* showed sensitivity to imipenem and cefixime, whereas *Gardnerella vaginalis* showed sensitivity to meropenem (100%) and imipenem (100%). MRSA strains were sensitive to ceftazidime (60.9%) and cefpodoxime (60.9%).

Discussion

Vaginal infections have wide implications for women's health, being the most common gynaecological problem.[12] It is believed that the lactobacilli play an important role in maintaining normal vaginal ecosystem and preventing the growth of opportunistic bacteria.[13] Our study demonstrates the prevalence of potential vaginal pathogens in symptomatic women.

The results of our study are comparable to the study by Lakshmi K et al., which compared the prevalence of vaginal infections between premenopausal and postmenopausal women.[14]

Increased infections in post-menopausal women are due to the vagina being colonised by pathogenic organisms more than the protective organisms.[15] The highest frequency of infection was noted at an age of 20 to 30 years with a fall in the frequency of infection as age advanced. Similar results with respect to age were seen in a Kenyan study, although it was limited to the study of only one organism.[16]

Several microorganisms were isolated in our study, and those with the highest frequencies were *Escherichia coli*, diphtheroids, *Klebsiella pneumoniae*, *Streptococcus agalactiae*, *Pseudomonas aeruginosa*, *Proteus vulgaris*, MRSA, Micrococci, Enterococci, Acinetobacter, Citrobacter and *Candida albicans*. Commensal growths were found in 14% of cases that need not be treated, but necessary measures such as identification of risk factors (douching, sprays, diabetes) and their prevention have to be carried out.

We also found *Escherichia coli* to be the most common pathogenic bacteria (11.5%) isolated from culture. In fact, *Escherichia coli* was found to be the most prevalent pathogen isolated not only from high vaginal swabs but also urine, pus, blood and wounds, as seen in a study conducted by Dutta S et al., in Dhaka.[17]

Candida albicans is tolerant to the acidic environment and is hence found in the vagina, but the concentrations are too low to cause symptoms. In conditions of decreased local immunity, the hyphae would multiply and transform into infective patterns that result in symptomatic vaginitis.[18] Colonization of Candida species also happens during pregnancy, resulting in symptomatic vaginitis.[19]

Infections with MRSA became a global health issue in 1960s, when the strains were first identified. They may be acquired nosocomially or from the community. What make them difficult to treat are their multiple antibiotic resistant profiles and wide varying prevalence.[20] One should keep in mind that higher antibiotics may be required to treat these infections.

In our study, 6% of the women carried *Streptococcus agalactiae* (Group B Streptococci). However, information regarding their pregnancy status is not available. Maternal group B Streptococci (GBS) colonisation is a major risk factor for GBS disease in neonates.[21] In pregnant women, GBS causes cystitis, amnionitis, endometritis and stillbirth; occasionally, it leads to endocarditis or meningitis.

Coagulase-negative Staphylococci (CoNS), which are considered to be skin commensals, were found in 4% of the cases. No cases of trichomoniasis, Chlamydia infection, and *Neisseria gonorrhoeae* infection were noted.

The presence of co-morbidities like hospitalization, immunosuppression and co-existent reproductive tract infections have to be evaluated accordingly. It is known that vaginal infections, due to a disruption of normal vaginal flora, increase the risk of sexually transmitted infection, especially human immunodeficiency virus (HIV).[22] However, our study did not identify any association with HIV, and diabetic status records were not available. No patients had taken hormone supplements or any other medications that could interfere with the results.

Our study has several limitations. The practice of swab culture is done mostly in clinical microbiological laboratories, and clinical diagnosis may be suboptimal. Only regularly used antibiotics were included in the sensitivity testing, and socio-demographic factors have not been considered. These limitations have to be overcome by future studies, and proper practices have to be implemented in order to preserve these lifesaving drugs for the future.

Diagnosis of these infections based on culture sensitivity is a definite step in treatment of these infections. In regular practice, fixed protocols are followed. Inadequate treatment with antimicrobials due to non-compliance or under the prescription of drugs results in high incidence of recurrence. Extensive resistance rates have emerged among commonly used antibiotics due to indiscriminate use. Newer antibiotics like imipenem and meropenem are highly effective but expensive.[23] Short term effects of antimicrobial regimens have been tested and proved through clinical trials to be effective in achieving clinical and microbiological cure. Newer therapeutic approaches include the development of new drugs, phage therapy (bacterial viruses can be robust anti-bacterial agents in vitro), photodynamic inactivation of micro-organisms and immunomodulators.[24] A significant proportion of pathogens causing vaginal infections are resistant to the conventionally used antibiotics. This study is a step in familiarizing sensitivity and resistance patterns to used antibiotics, preventing resistance and thus preventing the chronic sequelae. Thus, we raise a question of changing the syndromic protocol to treatment protocol based on culture sensitivity. Substantial health gains with a reduction of the disease burden among women should be the long term goal of treatment which should be intended with knowledge of culture sensitivity.

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Acknowledgments

Our sincere gratitude to Dr Padmasri Ramalingappa, Professor and Head of Department of Obstetrics and Gynecology, and Dr Urvashi Bhatara, Assistant Professor of Obstetrics and Gynecology at Sapthagiri Institute of Medical Sciences and Research Center, for their continuous support and inspiration throughout the work.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

Conception and design the work/idea, Contribution of patients or study material: PR, UB. Collect data/obtaining results, Write the manuscript: NNS. Analysis and interpretation of data, Critical revision of the manuscript: NNS, PR, UB. Statistical advice: UB.

Cite as:

Narayana-Swamy N, Ramalingappa P, Bhatara U. Antimicrobial Sensitivity Pattern of Microorganisms Isolated from Vaginal Infections at a Tertiary Hospital in Bangalore, India. Int J Med Students. 2014 Nov-2015 Mar;3(1):34-9.

IJMS International Journal of Medical Students

Original Article

A Pilot Study of the Effect of a Change in the Scheduling of Canadian Medical Licensing Examinations on Two Cohorts of Students Studying in Ireland

Kate Niethammer,[1] Pishoy Gouda,[2] Edina Moylett.[3]

Abstract

Background: The Medical Council of Canada and most Canadian residency programs require international medical graduates seeking training in Canada to pass the Medical Council of Canada Entrance Examination, in addition to the newly established National Collaborative Assessment. In order to facilitate this additional examination, the Medical Council of Canada has altered the suggested examination timeline and examination eligibility criteria. **Methods:** A cross-sectional survey was sent via an online survey tool to members of the North American Irish Medical Student Association. The survey aimed to elicit differences in the Medical Council of Canada Entrance Examination experience between two cohorts of Canadians studying abroad in Ireland: those who completed the examination before and after the new timeline. Statistical analysis was conducted with independent t-tests and Pearson's Chi-Square tests using SPSS version 21. **Results:** Of 24 respondents, 13 had completed the examination after the timeline change. Participants who attended the examination prior to the change achieved higher results (353.8 ± 56.5) than participants who attended the examination after the change (342.3 ± 35.1), although not statistically significant (p=0.56). In the cohort who took the examination after the timeline change, 61.5% of participants expressed discontent with their examination results; 84.6% 'strongly agreed' or 'agreed' to feeling disadvantaged due to the change. **Conclusion:** The new Medical Council of Canada examination timeline has had an impact on the examination experience of Canadians studying in Ireland. Simple modifications to the current timeline are warranted to reduce unnecessary disadvantage for this cohort of students applying to postgraduate training in Canada.

Keywords: Students, Medical; Education, Medical; Educational Measurement; Education; Emigration and Immigration (Source: MeSH-NLM).

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Introduction

In order to preserve a high standard of health care providers in Canada, the Medical Council of Canada (MCC) requires that international medical graduates (IMGs) seeking postgraduate training in Canada pass several entrance examinations. These checkpoints were developed to ensure a high level of knowledge required to succeed in postgraduate training. These examinations include the Medical Council of Canada Entrance Examination (MCCEE) and the newly established National Collaborative Assessment (NAC) Objective Structured Clinical Exam (OSCE). These examinations must be completed prior to sitting the Medical Council of Canada Qualifying Exam (MCCQE) I and II (Medical Council of Canada. Available from: http://mcc.ca/examinations/nac-overview/application-information/#Timing, updated 2015, cited 2015 Feb 16).

Prior to the establishment of the NAC OSCE, medical students studying abroad, many of whom are Canadian citizens, sat the MCCEE in their final year of study in order to apply for residency positions through the Canadian Residency Match System (CaRMS). Prior to the 2015 CaRMS cycle, only a select number of provinces (British Columbia, Alberta, and Quebec) required the completion of the NAC OSCE in order to apply to their postgraduate training programs. Since then, additional provinces (all except Saskatchewan) have added the NAC OSCE as an eligibility requirement (Canadian Resident Matching Service. Available from: http://www.carms.ca/en/match-process/your-application/match-tips/nac-osce/, updated 2015, cited 2015 Feb 16). Due to this change, the MCC has made significant changes to the examination timeline and requirements (***Figures 1***).

In order to be eligible to sit the NAC OSCE, applicants must have received a pass result in the MCCEE prior to the application. Therefore, the latest an applicant could sit the NAC OSCE, to be eligible for the CaRMS match, is the September prior to the match. To ensure eligibility for the September sitting, the MCC suggests that candidates write the MCCEE no later than March, one year before the expected match.

For Canadian IMGs, referred to as Canadians studying abroad (CSAs), this change in the timeline has caused significant challenges to the process of applying to postgraduate training in Canada unique to this cohort of IMGs.[1] CSAs are now required to write the MCCEE half way through their penultimate year, which means that many applicants will not have had exposure to the core clinical rotations covered in the exam, further complicating an already difficult process.[2] While the difficulties of immigrant physicians in Canada are well documented, there is sparse information regarding the return migration of CSAs.[3]

In 2010, there were an estimated 3,500 Canadian students studying medicine abroad, with more than 700 of them stud-

Submission: Feb 16, 2015
Acceptance: Mar 24, 2015
Publication: Mar 31, 2015
Process: Peer-reviewed

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ying in Irish medical schools;[4] 90% of CSAs have indicated a desire to return to Canada for postgraduate training.[5] Foreign medical schools are seeing an increasing trend in Canadian students' enrollment,[6] without a guarantee of local postgraduate training.[5] This has created a highly competitive field for the limited number of residency positions designated for IMGs in Canada, with only 25% of IMG candidates successfully matching to residency positions in Canada in 2010.[6] The positions available frequently require a return of service contract that are vital to ensure that many underserved, rural physician posts are filled.[7] Nonetheless, Canada has still been described as underutilizing IMGs by IMGs and their families.[8]

This study aims to describe the differences in the MCC certifying examination experience between two cohorts of Canadian medical students in Ireland, comparing those who completed the exam prior to and those following the implementation of the new examination timeline. Our results may be used to inform the debate on the appropriateness of the newly implemented timeline, as well as student feedback on the effects of these changes. There is currently no reported literature on the subject.

Due to students being required to write the MCCEE earlier than previous students studying abroad, we hypothesized a decrease in the average scores and a more negative examination experience in the post-change cohort.

Methods

In April 2014, a cross-sectional survey was sent out to the 746 members of the North American Irish Medical Student Association (NIMSA). Representatives from each medical school were contacted via email and requested to contact all eligible Canadian students in their final or penultimate year studying at their school (n=288). All candidates were provided a URL to the survey hosted on an online survey tool (http://www.surveymonkey.net). Due to the methods of distributing the survey and having no central database of Canadians studying in Ireland, it is difficult to confirm if all students eligible to partake in the survey received it.

Participation was voluntary, and students were allowed to discontinue at any stage of the study. Students were assured at multiple stages of the study that their responses were anonymous. The survey remained open for six months.

The questionnaire aimed to elicit methods of preparation for the MCCEE, MCCEE results, as well as personal satisfaction with the exam experience and results. The survey contained a combination of nominal, ordinal, and scale items.

Statistical analysis was conducted using the independent t-test to describe score differences between the two cohorts. Pearson's Chi-Square test was used to compare MCCEE exam experience between the two cohorts. The Statistical Package for Social Science (SPSS) software version 21 was used for data analysis.

Ethical approval was granted by the Research Ethics Committee at the National University of Ireland, Galway on July 4, 2014 (Number 2014-06-12).

Results

Participant Demographics

Out of the potential 288 students in final and penultimate year of study, 24 participants completed the survey. Fourteen (58.3%) were female, and the average age was 27.4 years. Thirteen (54.2%) participants wrote the MCCEE following the change to scheduling. Sixteen (66.7%) of participants were enrolled in an undergraduate medicine course, the remainder post-graduate. Based on academic record, the majority of participants were of 2nd class honors standard (20/24). (***Table 1***).

MCCEE Preparation

The majority of students (54.2%) studied 20-39h per week in the month leading up to the exam; nine participants (37.5%) 0-19h per week, one (4.2%) 40-59h and one studying more than 60 hours per week. Eight (37.5%) students reported using only online question banks; the remainder (66.7%) used a mixture of questions banks and textbooks. There was no reported difference in study method or study hours between the pre-change cohort and the post-change cohort. Nine participants (37.5%) stated that they did not complete rotations in all the examined clinical disciplines of the MCCEE (Medicine, Surgery, Psychiatry, Pediatrics, and Obstetrics and Gynecology); the vast majority (88.9%) of them were participants in the post-change cohort.

MCCEE Results

Self-reported scores were available for nearly all participants (95.8%). All participants passed the exam (250 is the standardized pass mark). The average mark obtained was 347.8 ± 45.9 (Standard Deviation, SD). Female participants were non-significantly more likely to achieve a higher result than male participants (355.5 ± 48.0 vs. 335 ± 42.2, p=0.33). Participants in the pre-change cohort were also non-significantly more likely to achieve higher results than participants in the post-change cohort (353.8 ± 56.5 vs. 342.3 ± 35.1, p=0.56).

Reflection on MCCEE Experience

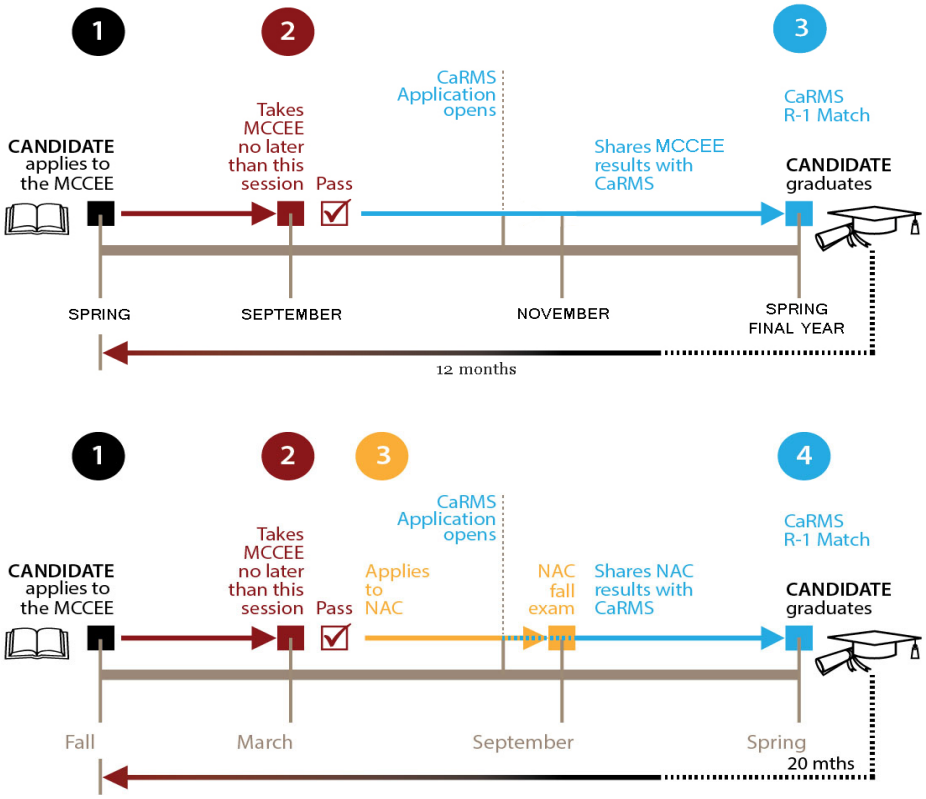
Concerning the statement, "Did you feel like you had enough time to prepare for the exam?" three (12.5%) participants 'Strongly Agreed', 10 (41.7%) 'Agreed', two (8.3%) neither 'Agreed or Disagreed', five (20.8%) 'Disagreed' and four (16.7%) 'Strongly Disagreed'. While not statistically significant, a higher proportion of post-change students (23.1%) 'Strongly Disagreed' that there was enough time to prepare compared to pre-change students (9.1%) (p=0.35).

Regarding satisfaction with MCCEE results, in the post-change group, 61.5% either 'Disagreed or Strongly Disagreed' with the statement that they were pleased with their result, compared to only 18.2% of the pre-change group (p=0.10).

Table 1. Participant Demographics Information.

Characteristic	Pre-Change Cohort (n=11)	Post-Change Cohort (n=13)
Female (%)	8 (72.7%)	6 (46.2%)
Age (Mean ± SD)	27.4 ± 2.0	27.3 ± 3.0
Postgraduate (%)	4 (36.4%)	4 (20.8%)

Figure 1. Previous (top) and Current (bottom) Canadian Residency Match System R1 Match Timeline.



Discussion

Of the 24 students that participated in this study, 13 sat the examination post schedule change. The majority (61.5%) of those in the post schedule change group had not completed the core rotations and topics tested in the MCCEE. As hypothesized, our study showed that lower average examination results were attained in the post-change group, although not statistically significant. This may, in part, be explained by the fact that this cohort sat the MCCEE with a large part of their clinical education still ahead of them.

Despite no recorded difference in the nature of designated study time, we found that students were negatively affected by the earlier exam date. As hypothesized a higher proportion of post-change students chose 'Strongly Disagree' when asked if there was enough time to prepare for the MCCEE. The majority of students' who stated that they were not pleased with their scores and felt disadvantaged with the timing of the exam in the medical degree were in the post-change cohort.

Overall, the change in the MCCEE timeline negatively affected CSAs studying in Ireland who sat it prior to March 9th, 2014. The students who sat the exam after the change in their penultimate year received overall lower scores, felt less prepared and were not pleased with their score results, although these findings were not statistically significant.

Prior to the examination scheduling change, students typically completed the examination in the September sitting, allowing them to prepare over the summer. By contrast, prospective residency applicants are now suggested to apply for the February/March sitting of the exam. It must be noted that this new suggested date falls in the period where students are full-time clinical clerks and have to meet the demands of their clinical education while studying for the MCCEE.

Residency programs receive hundreds of applications for a limited number of positions. It is a common practice to use cut off points to filter applications for further consideration, with MCCEE score being used as one of these.[9] Applicants who score below a certain threshold will not have the remainder of their application considered. This has several implications. If students proceed with the currently suggested timeline, and as suggested by our study, are not pleased with their scores, there is no opportunity to repeat the examination. If, in fact, the changes in the examination timeline result in widespread lower scores for CSAs, many qualified students will not even be considered for residency positions in Canada. Due to this possibility, the authors feel that it is appropriate that further discussion takes place with residency programs and regulatory medical bodies in Canada to ensure that everyone involved is aware of the changes. The authors would suggest that due to the new scheduling of the MCCEE, scores of the examination should be interpreted with care, as it is unlikely to reflect the clinical knowledge that the candidate will possess at the end of their clinical training. This is supported by a lack of correlation between MCCEE scores and the NAC OSCE, which examines clinical skills,[10] and studies showing a stronger correlation between structured clinical assessment results and IMG competence.[11] Data have also demonstrated that using the CaRMS application process, which includes records of students' marks, clinical experience, extra-curricular activities, reference

letters and personal statements in choosing applicants, is a better predictor of residency performance, when compared to using exam scores alone for applicant selection.[7]

Strengths and Limitations

Our study is the first to evaluate the examination experience of a subset of IMGs, the CSAs, in the process of applying to postgraduate training in Canada. However, there are limitations to our study. There is no centralized process to track medical students in Ireland taking Canadian licensing examinations, making it difficult to ascertain if all students who wrote the examination received the questionnaire.

The Health Education Authority of Ireland has shared with the authors that during the 2013/2014 academic years, there were 122 final year Canadian medical students studying in Ireland and 166 penultimate year Canadian medical students in Ireland. These figures represent the greatest possible number of individuals who were eligible to sit the MCCEE. Using these figures, our study represents 8.3% of this cohort, which is a conservative figure, considering that of the theoretically eligible 288 students, many will not have registered for the exam for a variety of reasons. While our sample size is small, it greatly surpasses the sample size required for a pilot study.[12] This represents only a sample of CSAs in Ireland, but indicates that the full extent of the issue could be further explored in the future.

Finally, all exam results are self-reported and, therefore, an exaggeration bias must be considered. However, survey participants were reassured that the survey was completely anonymous. As the authors expected a small sample size the decision was made to not collect the institution of applications to further add to anonymity, which was relayed to survey participants.

Recommendations

Despite showing no statistically significant differences in exam scores between the two cohorts, our study highlights some of the effects of the new scheduling of Canadian entrance exams. We would recommend that the Medical Council of Canada consider the impact of this change has on the selection of future residents. If students were not required to have passed the MCCEE prior to writing the NAC, then they would be able to sit both of these exams in September of their final year. This would ensure that more applicants would have completed core rotations in the topics tested. In addition, this suggested timeline would provide candidates with more designated time during the summer to study for both exams while still meeting the requirements for applying for residency positions in Canada.

Residency program directors in Canada should also be made aware of the changes in the scheduling. If the program directors or member of the selection committee were not trained outside of Canada, they might be unaware of the change in the application process for CSAs applying to Canadian residency programs. This may have considerable effects on the way that program directors interpret MCCEE results and re-evaluate its use as a cut off factor.

Our study has identified several issues with the change in the MCC's schedule of the MCCEE for IMGs, particularly the CSA subset. To explore the issues raised in this pilot study, we propose that a large-scale study, supported by the MCC, is necessary to address and justify the changes caused by the examination scheduling on a unique and important cohort of IMG applicants, the CSAs.

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Acknowledgments
None.

Conflict of Interest Statement & Funding
The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea: KN, PG, EM. Collect data/obtaining results, Analysis and interpretation of data, Write the manuscript: KN, PG. Critical revision of the manuscript, Approval of the final version: KN, PG, EM.

Cite as:
Niethammer K, Gouda P, Moylett E. A Pilot Study of the Effect of a Change in the Scheduling of Canadian Medical Licensing Examinations on Two Cohorts of Students Studying in Ireland. Int J Med Students. 2014 Nov-2015 Mar;3(1):40-4.

Mitochondria as a Target for Future Diabetes Treatments

Franziska Thimm,[1] Marten Szibor.[2]

Abstract

Diabetes mellitus is rapidly becoming the world's most dangerous serial killer. Type 1 diabetes (T1D) is a currently incurable autoimmune disease marked by progressive, and eventually exhaustive, destruction of the insulin-producing pancreatic beta cells. Type 2 diabetes (T2D) describes the combination of insulin resistance in peripheral tissue, insufficient insulin secretion from the pancreatic beta cells, and excessive glucagon secretion from the pancreatic alpha cells. T1D as well as severe cases of T2D are treated with insulin replacement, which can merely be considered as life support for the acute phases of the disease. Islet replacement of insulin-producing pancreatic beta cells represents a potential treatment method for both insulin-depleted diabetes (T1D) and insulin-resistant diabetes (T2D) and may shift diabetes management from life saving measures to a cure. One of the key challenges in islet transplants is the generation of reactive oxygen species (ROS) and the associated oxidative stress, which restricts graft longevity. A major leak of ROS takes place during oxidative phosphorylation at mitochondrial electron transport chain (ETC). Additionally, hyperglycemia-induced superoxide ($O_2^{\bullet-}$) production has been linked to the development and progression of diabetic complications, both macrovascular and microvascular. Decreasing ROS in diabetic patients may prevent the incidence of long term diabetes complications. This review provides an overview of the role of mitochondria in diabetes, introducing them as a possible target for future treatment of diabetes.

Keywords: Reactive Oxygen Species, Mitochondrial DNA, Diabetes Mellitus, Electron Transport, Oxidative Phosphorylation (Source: MeSH, NLM).

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Introduction

The definite etiology of type 1 diabetes (T1D) is still obscure, but considered to root in a mixture of genetic predisposition and environmental factors, leading to continued autoimmunity.[1] Five percent of diabetics have this type of diabetes.[2] In Type 2 diabetes (T2D), peripheral tissue develops a resistance against insulin.[3] T2D has been linked to "metabolic syndrome", which is defined by the International Diabetes Federation (IDF) as central obesity with two of the following: elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density cholesterol (HDL) levels (Available from: http://www.idf.org/metabolic-syndrome, updated 2014 Oct 23; cited 2015 Jan 21). According to the Centers for Disease Control and Prevention (CDC), one out of three people will develop T2D in their lifetime.[2]

The aims of diabetes management are primarily to save life in the short term and secondarily to prevent the development of diabetic complications in the long term. Both can be achieved by improving glycemic control, aiming for a glycated hemoglobin (HbA1c) between 6.5%-7.0%.[4] For patients with T1D, lifelong insulin replacement therapy marks the therapeutic objective for attaining glycemic control.[5] In T1D, insulin dose varies between 0.4–0.8 UI/kg insulin a day.[6] However, insulin administration may induce hypoglycemic episodes that require hospitalization. The fear of hypoglycemia and the inconvenience of daily insulin injections cause many patients to neglect proper disease management and experience glycemic lability.[7]

For the management of T2D, lifestyle adjustments are considered the mainstay. If glycemic control fails to be obtained by lifestyle changes, treatment may resort to oral hypoglycemic agents (OHA), including biguanides, sulphonylureas, alpha glucosidase inhibitors, and thiazolidinediones. In severe cases, insulin injections are required. If indicated, T2D patients need between 0.2–1.6 UI/kg of insulin a day.[5] The current treatment options available for both types of diabetes merely delay the complications of the disease and do not provide a long-term solution.

Islet replacement of insulin-producing pancreatic beta cells represents a potential treatment method for both insulin-depleted and insulin-resistant diabetes.[8] Following islet transplantation the patients benefit not only from a decrease of hypoglycemic events, but also spectacular improvement of HbA1c levels and stabilization of fasting blood glucose, without exposing themselves to the risk of major surgery as in whole pancreas transplantation.[8] A study by Barton and colleagues compared the efficacy of allogenic islet transplantation in T1D patients in different periods between 1999 and 2010.[9] They analyzed 677 T1D patients who had received islet transplants, with the aim to examine the differences in transplant efficacy between the early (1999-2002), mid (2003-2006), or recent (2007-2010) transplant era. Three years following the islet replacement, insulin independence improved from 27% in the early era to 37% and 44% in the mid and recent eras, respectively, at 36 months after transplantation. Barton and colleagues suggested that the

Submission: Aug 24, 2014
Acceptance: Jan 26, 2015
Publication Feb 22, 2015
Process: peer-reviewed

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improvement of graft survival can be linked to more adequate means for preventing islet rejection.[9] One of the key challenges in islet transplantation is the generation of reactive oxygen species (ROS) and the associated oxidative stress.[9] Oxidative stress occurs due to an imbalance between the intracellular free radical production and the cellular antioxidant defense mechanisms in the transplanted islets, which can lead to cell death. The cellular antioxidant defense mechanism comprises, among others, vitamins and minerals that are hence administered as supplements after organ transplantation.[10] But why not directly target the chief generator of oxidative stress in our cells? Our mitochondria constitute the major ROS generator, as ROS are released as a byproduct of oxidative phosphorylation in the electron transport chain (ETC) of the inner mitochondrial membrane (IMM).

This review provides an overview of the correlation between mitochondria and diabetes, introducing them as a target for future treatment of diabetes.

Search Strategy and Selection Criteria

A literature search was performed using MEDLINE MeSH terms "reactive oxygen species", "alternative oxidase", "mitochondrial DNA", "diabetes mellitus", "respiratory chain" and "oxidative phosphorylation". A total of 9807 articles were found. Following filtering based on selection criteria (publication within last 20 years, English language, and the condition that at least 4 of the given terms must be in the same article), 7 articles remained and an additional 13 articles were retrieved from references. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[11]

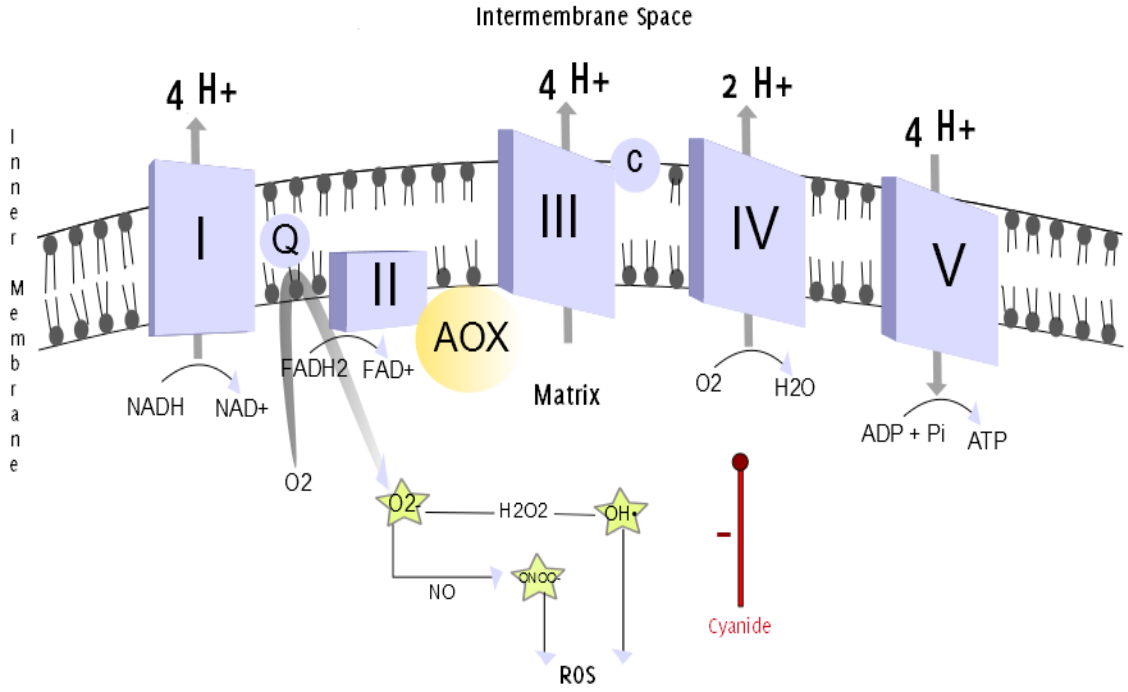
The Powerhouse of the Cell

Mitochondria are of prokaryotic origin and now the powerhouse in eukaryotic cells. The term was coined by a pioneer in modern cell biology, Philip Siekevitz, and reflects a critical role of the organelle, which is energy generation by aerobe degradation of nutrients.[10] Mitochondria are enclosed by a double membrane system, the outer mitochondrial membrane (OMM), and the inner mitochondrial membrane (IMM), each reflecting its function through its respective structure.[12]

Metabolic energy is derived through a process known as oxidative phosphorylation. The proteins required for this process are embedded in the IMM. The surface area that is required to accommodate the proteins that participate in this process is provided by the configuration of the IMM into crista (***Figure 1***).[12]

Substrate oxidation and adenosine triphosphate (ATP) production [phosphorylation of adenosine diphosphate (ADP)] are coupled and commonly referred to as "oxidative phosphorylation".[12] During oxidation, electrons are transferred from redu-

Figure 1. The Mitochondrial Respiratory Chain.



Legend: The mitochondrial respiratory chain. The efflux of protons from the mitochondrial matrix into the intermembrane space establishes an electrochemical gradient. The back movement of protons down the electrochemical gradient is utilized by complex V/ATP Synthase (a proton channel) to phosphorylate ADP, and produce ATP. Oxidation and phosphorylation are coupled. The uncoupling of the processes can be achieved when uncoupling substances allow protons to pass through the IMM through an alternative pathway, without passing through complex V.[13-14] This can be realized by the uncoupling protein *thermogenin*, which is present in brown adipose tissue. This alternative flow results in thermogenesis, the production of heat, rather than the ATP generation.[15] In neonates, *thermogenin*-containing brown adipose tissue makes up to 5% of the body mass and is located primarily on the back. This can be explained evolutionarily, as the infant's back was exposed to the environment during breast feeding and at higher risk of hypothermia.[16] AOX provides an alternative pathway for electrons passing through the respiratory chain, directly converting O2 into H2O, bypassing complexes III and IV. *Antimycin* and *cyanide*, inhibitors of complex III and complex IV, respectively, are therefore ineffective during activation of AOX. Superoxide ($O_2^{\bullet-}$) anions are produced when Coenzyme Q donates unpaired electrons to molecular oxygen.[17] The reaction between $O_2^{\bullet-}$ and NO produces peroxynitrite ($ONOO^{\bullet-}$). Hydrogen peroxide (H_2O_2) is converted into a hydroxyl radical ($OH^{\bullet}$). Both $O_2^{\bullet-}$ and $ONOO^{\bullet-}$ are powerful oxidants.[18]

ced coenzymes (nicotinamide adenine dinucleotide in its reduced form, NADH, and flavin adenine dinucleotide in its reduced form, FADH2) via the ETC to molecular oxygen as a final electron acceptor. The "chemiosmotic hypothesis" of oxidative phosphorylation postulates that during the electron movement, released energy is used by complexes I, III, and IV to facilitate the transport of protons from the matrix to the intermembrane space (IMS).[19]

The proton movement establishes an electrochemical proton gradient (delta Psi, ΔΨ) (180-190 mV negative to the cytosol),[13] that is subsequently equalized by H+ movement through a gateway of the IMM – "ATP synthase". Like in a watermill, the "molecular unit of currency" or ATP is generated by the movement of protons down their electrochemical gradient through ATP Synthase.[14]

Oxidative Stress in Diabetes

Oxidative stress makes up two crucial puzzle pieces of diabetes. First, hyperglycemia-induced long-term complications of diabetes occur due to excessive production of ROS.[20] Second, if scientists are successful in decreasing ROS generation after pancreatic islet replacement, prolonged graft survival could be ensured and diabetes treatment would shift from being life sustaining to achieving a cure.

Glucose metabolism uses the Krebs cycle to generate NADH and FADH2, which donate electrons to complex I and complex II, respectively. These electrons are subsequently passed down the ETC to molecular oxygen as a final electron acceptor, a process which facilitates proton movement across the IMM. Glucose laden, diabetic cells exhibit a higher rate of glucose oxidation in the Krebs cycle, triggering more NADH and FADH2 being shoved into the ETC and ultimately establishing a higher ΔΨ across the IMM. Eventually the electrical gradient will reach a threshold, and the electron transfer in complex III will be inhibited, resulting in the backup of electrons to coenzyme Q. Coenzyme Q then donates unpaired electrons to molecular oxygen, thereby generating the free radical O2•-.[22]

Under the influence of superoxide dismutase (SOD), O2•- can become a weaker ROS, hydrogen peroxide (H2O2).[23] However, when O2•- reacts with nitric oxide (NO•) it may also be converted into the more active ROS peroxynitrate (ONOO-) (***Figure 1***).[20] Both O2•- and ONOO•- are powerful oxidants.[23]

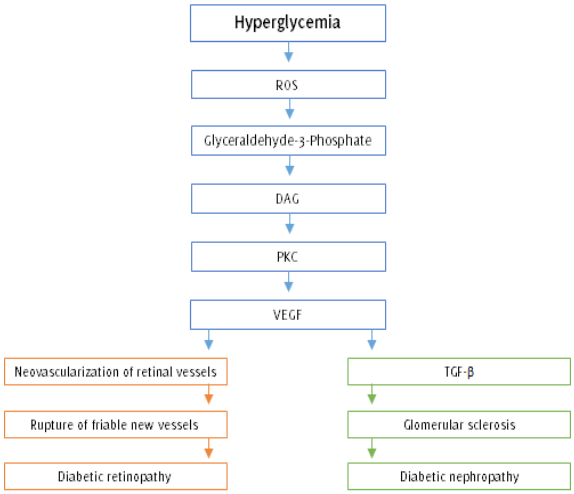
Furthermore, hyperglycemia-induced O2•- generation in the mitochondria decreases the activity of glyceraldehyde-3 phosphate dehydrogenase (GAPDH), an enzyme that serves as the catalyst for the sixth step of glycolysis and is essential for glucose production from glycogen breakdown (glycogenolysis).[20,24] The inhibition of GAPDH results in the accumulation of glyceraldehyde-3 phosphate, and the activation of the hyperglycemia pathways described hereafter in detail [protein kinase C (PKC) pathway; advanced glycation end-products (AGE) pathway].[20]

The PKC pathway is initiated by the presence of a derivative of glyceraldehyde-3 phosphate, diacylglycerol (DAG). Excessive intracellular DAG stimulates PKC, a kinase protein that induces vascular endothelial growth factor (VEGF) expression in non-vascular cells.[25] VEGF is an essential angiogenesis factor and key to neovascularization. The VEGF-mediated neovascularization of the retina is a process known to play role in diabetic retinopathy. In diabetic retinopathy, the genesis of friable vessels that frequently rupture results in hemorrhages that obscure the vision.[26] VEGF also increases levels of transforming growth factor beta (TGF-ß), which is profibrinogenic and accelerates progression to glomerular sclerosis and hypertrophy, contributing to diabetic nephropathy (***Figure 2***).[27]

Another derivative of glyceraldehyde-3 phosphate, methylglyoxal, activates the AGE pathway.[22] The hyperglycemia-induced AGE pathway generates AGEs by non-enzymatic glycation of proteins. AGE production is irreversible, and circulating AGEs contribute as a deteriorating factor to vascular complications of diabetes patients.[25]

Circulating AGEs are involved in the trapping of albumin, low-density lipoprotein (LDL), immunoglobulins, and complement components. This procoagulating effect of AGEs is further increased by its function to deactivate NO•, which leads to the loss of the vasodilatory effect of NO. Besides, AGEs function as procoagulants themselves through increasing platelet adhesion and, at the same time, decreasing fibrinolysis. Also, AGE molecules are capable of binding to RAGE receptors present on both macrophages and mesangial cells of the kidney. This binding stimulates the release of cytokines and growth factors, which results in inappropriate cell proliferation, collagen synthesis, and fibrosis in the glomeruli. Finally, AGEs spur lipid oxidation, which increases oxidative stress and favors inflammation.[28]

Figure 2. Hyperglycemia: The Role of Protein Kinase C Activation in Diabetes Complications.[21]



Legend: Hyperglycemia-induced O2•- generation in the mitochondria leads to the accumulation of glyceraldehyde-3 phosphate and its derivative DAG. Elevated intracellular DAG levels stimulate the PKC-mediated generation of VEGF, an angiogenesis factor that promotes neovascularization of retinal vessels. Unfortunately, the newly formed vessels are highly friable and would often rupture, resulting in hemorrhages that obscure the vision and destroy the retina (proliferative diabetic retinopathy). On the other hand, elevated levels of VEGF are responsible for simultaneously rising amounts of TGF-ß that spurs glomerular proliferation and sclerosis, eventually resulting in diabetic nephropathy (ROS = Reactive oxygen species; DAG = Diacylglycerol; PKC = Protein kinase C; VEGF = Vascular endothelial growth factor; TGF-ß = transforming growth factor beta).

Many experiments demonstrated that the inhibition of AGEs slow down the developments of diabetic retinopathy in laboratory rats.[29] Hammes and coworkers treated 26-week-old Wistar rats with aminoguanidine, an inhibitor of AGE formation. The induction of diabetes was achieved with an injection of streptozotocin in 0.05 M sodium citrate. The administration of aminoguanidine was initiated 2 weeks later. Advanced glycosylation-specific fluorescence enabled the scientists to visualize the amount of accumulated AGEs in the animals' retinal vessels in the 26th and 75th week. While no morphological changes and 170±15 fluorescence absorbance units were observed in the healthy animals after 75 weeks, the diabetic rats had a high degree of neovascularization with friable vessels and 440±20 fluorescence absorbance units. The retinal vessels of those diabetic animals that had received aminoguanidine injections were less affected by these morphological changes, and glycosylation product-specific fluorescence measured was only 220±13.[30] Although aminoguanidine has been under development as a drug by the pharmaceutical company Alteon, clinical trials have been abandoned since 1998.[31]

The inhibition of GAPDH also results in the accumulation of the first and second glycolytic metabolites, glucose and fructose 6-phosphate. Glucose is reduced by aldose reductase into sorbitol, which is further oxidized by the enzyme sorbitol dehydrogenase into fructose. This so-called polyol pathway leads to a decrease of reduced NADPH.[26] NADPH is a crucial cofactor in redox reactions throughout the body, including the synthesis of myoinositol in the kidneys (***Figure 3***). Myoinositol deficiency has been shown to be present in laboratory animals with induced diabetes as well as the sciatic nerve from deceased diabetic patients.[26]

Myoinositol is particularly important for the normal function of nerves. Already in 1987 it has been suggested by Salway and colleagues that myoinositol may prove valuable in preventing or delaying diabetic neuropathy. Neuropathy is marked by a slowed conduction velocity in peripheral and autonomic nerve fibers. Salway and his team, who had administered 500 mg myoinositol twice a day to seven different diabetes patients over a time span of two weeks, had observed an increased amplitude of the action potential of three different nerves (two in the lower extremity, one in the upper extremity). They suggested the possible value of myo-inositol in diabetes treatment in the future.[30]

In excess, ROS can activate several stress-sensitive intracellular signaling pathways (NF-kB, p38 MAPK, JNK/SAPK, and hexosamine) that induce gene expression. The products of these genes are involved not only in the development of diabetes complications, but also the development of insulin resistance.[32,33] For example, hyperglycemia-induced overproduction of $O_2^{\bullet-}$ diverts fructose-6-phosphate to the hexosamine pathway. The end product of the hexosamine pathway, UDP-N-acetylglucosamine is capable of glycating intracellular proteins, including transcription factors that alter gene expression (Available from: http://www.thepharmaletter.com/article/alteon-may-drop-pimagedine-in-niddm, updated 2014 Dec 21, cited 2015 Jan 21). This suggests that antioxidants could play a role in delaying and/or preventing the development of diabetes complications and insulin resistance, thereby immensely altering the pathophysiology of T2D.

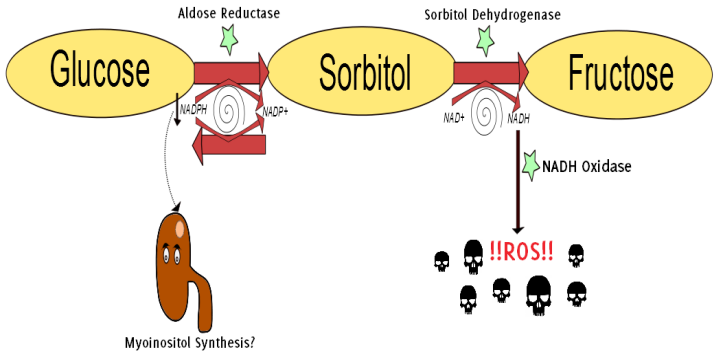
Alternative oxidase (AOX)

Alternative oxidase (AOX) is an integral mitochondrial membrane enzyme which is mainly found in sessile organisms. It is capable of limiting the overproduction of mitochondrial ROS. However, this alternative pathway bypasses several proton-pumping steps, decreasing the pH and electrical gradients, thereby reducing the ATP generation. During the course of evolution, AOX has been lost from fast-moving organisms (including humans), maybe due to the slight reduction in ATP production.[34]

By bypassing the respiratory chain, AOX confers resistance to cyanide and other inhibitors of the respiratory chain. Sessile animals, deep-sea organisms which are exposed to a hostile environment, thereby benefit from AOX and are still endowed with it.[34]

AOX provides a bypath of the ETC, thereby decreasing the $O_2^{\bullet-}$ generation and suppressing the infliction of oxidative damage on the cell. In the lab, AOX has been safely expressed in flies and human cells without eliciting any unwanted physiological side effects.[34]

Figure 3. The Polyol Pathway in Hyperglycemia.[35]



Legend: Hyperglycemia stimulates the aldose reductase-mediated reduction of glucose into sorbitol (a polyol, hence polyol pathway). Aldose reductase utilizes cofactor NADPH, which results in a depletion of the antioxidant glutathione (GSH) and increases intracellular oxidative stress.[31] Besides, NADPH is a crucial cofactor in redox reactions throughout the body, including the synthesis of myoinositol in the kidneys. Myoinositol deficiency has been identified in diabetic patients.[36] Sorbitol is further oxidized to fructose. The generated NADH is subsequently converted by NADH oxidase into ROS and, therefore, acts as a booster for oxidative stress on the cell.[37]

In 2013, *C. intestinalis'* (a sessile sea squirt) AOX gene was successfully expressed in mouse embryos with the help of germ line lentiviral transduction and subsequently passed down to the next generation.[38] This so-called MitAOX mouse could be crossed with selective lines of diabetic mice, for example the non-obese diabetic (NOD) mice, an animal model for T1D. The resultant diabetic mice should have AOX incorporated in their genome. This AOX incorporation could be helpful to investigate hyperglycemia-induced overproduction of $O_2^{\bullet-}$ and its role in the development of diabetic complications.

Additionally, it has been suggested that AOX mitochondrial targeting sequence could be delivered with the aid of a viral vector, especially since recent data clearly points to the longevity and safety of viral vectors.[34] This injectable AOX has the potential to allow for therapeutic application in many disorders with marked overproduction of $O_2^{\bullet-}$.[39]

Oxidative stress is influencing the allograft outcome during the peritransplantation period of kidney transplant.[38] In a study that Morales-Indiano and colleagues conducted on 131 patients with end stage renal disease (ESRD), both diabetic and non-diabetic patients had similar oxidative stress levels before kidney transplantation. However, measured oxidative stress was significantly higher in the diabetic patients after the intervention. In order to effectively measure oxidative stress, Morales-Indiano and colleagues determined and measured oxidative stress markers both prior to and at 120 days after grafting. The markers used to measure the generation of oxidative stress included anti-oxLDL antibodies (oxLDLab) and oxidized LDL. The poorer allograft function in diabetics was attributed to elevated HbA1C, which promotes oxidative stress.[17]

In future, AOX injections may be administered to decrease hyperglycemia-induced oxidative stress in diabetic patients after transplant, including pancreatic islet transplants.

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Acknowledgments
University of Helsinki, Mitochondrial Gene Expression and Disease group by Howard Jacobs.

Conflict of Interest Statement & Funding
The author has no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea, Collect data/obtaining results, Analysis and interpretation of data, Write the manuscript, Critical revision of the manuscript, Approval of the final version: FT, MS.

Cite as:
Thimm F, Szibor M. Mitochondria as a Target for Future Diabetes Treatments. Int J Med Students. 2014 Nov-2015 Mar;3(1):45-50.

Hepatorenal Syndrome in the Emergency Department: A Case Report

Win Jim Tan,[1] Mohan Tiruchittampalam.[2]

Abstract

Background: Hepatorenal syndrome is a condition where there is functional renal failure in a background of liver disease. It is relatively common in patients with liver cirrhosis and is associated with a high mortality rate if untreated. **Case:** This is a case report of an 88-year-old Chinese man presenting from a community hospital with a new onset of abdominal distension on a background of cryptogenic liver cirrhosis diagnosed on computed tomography scan. Clinical history and physical findings were consistent with that of fluid overload. Investigations performed indicated acute kidney injury together with liver failure secondary to liver cirrhosis. The patient was diagnosed with hepatorenal syndrome in accordance with the criteria established by the International Ascites Club and managed with an infusion of vasopressin and albumin in the emergency department. He was subsequently admitted to the general ward (gastrology), where he was managed for hepatorenal syndrome, improved clinically and was discharged to the nursing home. **Conclusion:** Hepatorenal syndrome can be managed effectively with albumin and vasopressin, and such treatment can be started as early as in the emergency department. Acute care physicians should not be hesitant in diagnosing and treating hepatorenal syndrome as early as in the emergency department for appropriate patients.

Keywords: Hepatorenal Syndrome, Liver Cirrhosis, Albumins, Vasopressins, Vasopressor Agents (Source: MeSH, NLM).

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Introduction

Hepatorenal syndrome (HRS) is a potentially reversible condition where there is functional renal failure in a background of liver disease. It is relatively common, with an incidence of 1 in 10 hospitalized patients with liver cirrhosis in the United States of America.[1] This is of great concern given the high mortality rate associated with HRS if left untreated. Type 1 HRS is associated with rapid progression to renal failure over as short a period as two weeks, compared to Type 2 HRS which is associated with a slow but steady progressive course with refractory ascites. Median survival time in patients with untreated type 1 HRS is two to four weeks, with 95% of such patients dying within the first 30 days of onset. Those with type 2 HRS have a median survival time of 6 months.[2] The International Ascites Club (IAC) has provided a set of criteria revised in 2005 to aid in the diagnosis of HRS (***Table 1***).

Given the high mortality rate associated with untreated HRS and the potential to reverse this syndrome, it is of utmost importance for clinicians to identify patients with HRS as per the IAC criteria and initiate appropriate treatment as soon as possible.[2] This report concerns a patient presenting to the emergency department of a tertiary hospital with HRS. This report serves to highlight the role acute care practitioners can play in diagnosing HRS and starting treatment early. The case reports statement (CARE) framework was followed in the drafting of this case report.

Key Points:

- Hepatorenal syndrome is a common complication of liver cirrhosis.
- If left untreated, hepatorenal syndrome, particularly type 1 with spontaneous bacterial peritonitis, is associated with a high mortality rate.
- Albumin and vasopressors have been proven to be a good treatment option for hepatorenal syndrome.
- Early institution of treatment is important in managing hepatorenal syndrome, and treatment may be instituted as early as in the emergency department.

Table 1. The International Club of Ascites Criteria for the Diagnosis of Hepatorenal Syndrome.

1. Presence of cirrhosis and ascites
2. Serum creatinine >1.5 mg/dL (or 133 µmol/L)
3. No improvement of serum creatinine (decrease equal to or less than 1.5 mg/dL) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (recommended dose: 1 g/kg b.w. per day up to a maximum of 100 g of albumin/day)
4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs
6. Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells/high power field, and/or abnormal renal ultrasound scanning

(Available from: http://www.icascites.org/about/guidelines/, updated 2005 Nov; cited 2014 Nov 16).

The Case

An 88-year-old Chinese man was referred from a community hospital when the caregiver noted abdominal distension while aiding the patient in rehabilitation. The patient had a past medical history of type 2 diabetes mellitus, hypertension, paroxysmal atrial fibrillation (PAF) and sick sinus syndrome for which he had a VVI pacemaker inserted, right hemispheric syndrome secondary to right middle cerebral artery infarction complicated by hemorrhagic conversion, and a background of

Submission: Jul 27, 2014
Acceptance: Nov 8, 2014
Publication: Dec 31, 2014
Process: Peer-reviewed

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cryptogenic liver cirrhosis corroborated with computed tomography (CT) findings which showed established liver cirrhosis and no evidence of obstructive nephropathy or parenchymal disease. He was on gliclazide and metformin for diabetes control, atorvastatin for dyslipidemia, amlodipine, enalapril and bisoprolol for hypertension, and aspirin for PAF. There was no recent change in medications.

On physical examination, the patient had anasarca, with a body temperature of 37.2 °C, pulse rate of 60 beats per minute, respiratory rate of 16 breaths per minute, blood pressure of 132/72 mmHg, and oxygen saturation of 100% on room air. The patient was drowsy, groaned and localized pain. His abdomen was soft and distended, with a positive fluid thrill and shifting dullness. Pitting edema was noted in bilateral lower limbs. Cardiovascular and respiratory examination yielded no significant findings, and the lungs were clear on auscultation. The patient was managed in the resuscitation area.

Hematological investigations were performed. Liver panel showed transaminitis with elevated alanine transaminase (ALT) at 78 U/L and aspartate transaminase (AST) at 77 U/L (***Table 2***). Renal panel showed markedly elevated urea at 37.8 mmol/L and mildly elevated creatinine at 133.0 µmol/L at presentation, rising from a baseline of 12.9 mmol/L for urea and 83.0 µmol/L for creatinine at one month prior to presentation. Mild hyperkalemia was also noted with a serum potassium level of 5.9 mmol/L. Other hematological investigations had values within normal ranges. Initial urinalysis showed no evidence suggestive of a parenchymal kidney disease, with the absence of proteinuria and microscopic hematuria. Analysis of the ascitic fluid ruled out occult sources of infection in this patient.

Differential diagnoses considered included fluid overload secondary to acute renal failure and deterioration of clinical condition secondary to underlying liver cirrhosis. The diagnosis of HRS could not be excluded based on the patient's clinical presentation. The patient had a background of cirrhosis and ascites and was not on any nephrotoxic drugs. He was not clinically in shock and was hemodynamically stable. Serum creatinine was elevated at 133.0 µmol/L with no evidence of parenchymal kidney disease. Considering the above clinical and laboratory findings together with the presentation of renal failure in a background of liver cirrhosis, the patient was provisionally diagnosed with HRS as per the IAC criteria (***Table 1***). With the prompt diagnosis, he was started on intravenous (IV) infusion of vasopressin at a rate of 0.01 U/min and albumin 5% in 500 ml over two hours. IV insulin at 5 U/h and IV dextrose 5% in 500 ml over eight hours were also started for the management of hyperglycemia. A nasogastric tube was also inserted for enteral nutrition given a previous history of dysphagia secondary to right middle cerebral artery infarction with hemorrhagic conversion.

In view of the diagnosis, the patient was admitted to the general medicine ward (gastrology). The patient's diagnosis of HRS was confirmed in the ward setting, and he was managed accordingly. He subsequently improved clinically and was discharged to a nursing home.

Discussion

This case report demonstrated that HRS can be diagnosed early and managed accordingly even in the acute care setting.[3] Diagnosis of HRS can be achieved with the aid of the criteria developed by IAC, and appropriate treatment can be started even before the patient is admitted to the ward.

The pathogenesis of HRS is currently still being explored. Arterial vasodilatation of the splanchnic circulation associated with the local release of vasodilatory substances is considered as a possible explanation. Renal vasoconstriction in the absence of reduced cardiac output and blood volume may also contribute to the development of HRS.[4] A high index of suspicion for HRS should be present in all cases with liver cirrhosis presenting with non-specific symptoms such as malaise and an acute decline in renal function.[2] It must also be noted that patients with type 1 HRS associated with spontaneous bacterial peritonitis have almost 100% hospital mortality rate if appropriate treatment is not provided.[5]

Given the wide variety of causes which may be associated with renal failure in patients with underlying cirrhosis, the IAC deve-

Table 2. Relevant Findings of Renal and Liver Function Tests and Urinalysis at Presentation and One Month Prior to Presentation.

Test	Reference Range	Feb 2014	Mar 2014
Urea, serum (mmol/L)	2.8 – 7.7	12.9	37.8
Sodium, serum (mmol/L)	135.0 – 145.0	135.0	146.0
Potassium, serum (mmol/L)	3.5 – 5.3	4.5	5.9
Chloride, serum (mmol/L)	96.0 – 108.0	109.0	119.0
Bicarbonate, serum (mmol/L)	19.0 – 31.0	17.0	15.0
Glucose, serum (mmol/L)	3.1 – 7.8	7.2	16.5
Creatinine, serum (µmol/L)	50 – 90	83	133
Albumin, serum (g/L)	37 – 51	N/A	24
Alanine transaminase, serum (U/L)	10 – 55	N/A	78
Aspartate transaminase, serum (U/L)	10 – 45	N/A	77
Red blood cells, urine (cells/high power field)	0 – 3	N/A	0
White blood cells, urine (cells/high power field)	0 – 6	N/A	13
Epithelial cells, urine (cells/high power field)	0 – 4	N/A	0
Protein, urine	Negative	N/A	Negative

loped a revised set of criteria in 2005 to aid in the diagnosis of HRS.[3] The utility of such criteria cannot be understated. With a 10% incidence rate among hospitalized patients and with the high morbidity and mortality associated with untreated HRS, early diagnosis and institution of appropriate treatment is of definite importance in these patients.[1,2,6]

The mainstay of therapy for patients with HRS remains liver transplantation. Published literature has shown the effectiveness of transplantation in ensuring survival and good renal function in patients with HRS.[7] It must however be noted that liver transplantation may not be suitable for all HRS patients. The unsuitability for liver transplantation, coupled with the long waiting times at most transplant centers, demands the search for alternative therapies for HRS.

Several pharmacological options are available in the management of HRS. While vasodilators such as dopamine were initially thought to be effective, the current practice has shifted to the use of vasoconstrictors. Several studies have shown that vasoconstrictors acting on the splanchnic circulation, including vasopressin and its analogues terlipressin and ornipressin, are able to improve patient outcome. It is postulated that these vasoconstrictors have an effect on the splanchnic circulation, reversing the vasodilatory effect usually found in HRS.[8] Despite a trial showing that terlipressin is more effective than norepinephrine in treating HRS, the utility of norepinephrine and other similar drugs as an alternative must not be discounted.[9]

The use of albumin together with vasopressors has also been shown to provide a good outcome, particularly in patients diagnosed with type 1 HRS associated with spontaneous bacterial peritonitis.[5] The IAC has recommended the use of albumin as the preferred volume expander in patients with HRS.[3] For this reason, a combination therapy involving both albumin and a suitable vasopressor such as terlipressin should be considered when initiating pharmacological management of HRS.

The strengths of this case report include the fact that there is little literature regarding prompt diagnosis and treatment of HRS, particularly in the acute care setting. We demonstrated that HRS can be diagnosed promptly using the criteria developed by IAC and managed accordingly even in the acute care setting. As the corroborative literature mentioned in the discussion has shown, early measures to tackle HRS are important in providing a better outcome for these patients.

We acknowledge the limitations of our case report. Given that this patient was managed in the acute care setting, the luxury of time was not afforded to us in our management of the case. Hence, the primary priority in this case was to provide acute care for the patient and to stabilize him for further treatment by the gastrologist in the ward setting. In this instance, other investigations such as ascitic fluid analysis to rule out spontaneous bacterial peritonitis could only be performed after the patient was transferred to the ward.

Conclusion

Several learning points can be obtained from this case report. From the above discussion regarding medical literature concerning HRS, early diagnosis and initiation of appropriate treatment is definitely important in managing HRS. Acute care clinicians should consider HRS as a possible diagnosis in patients presenting with a new onset of renal failure and with a background of liver cirrhosis. Albumin and vasopressors can and should be started as early as in the emergency department in patients who are suspected of having HRS. Acute care physicians should not be hesitant in diagnosing and starting the treatment of HRS in the appropriate patients particularly in the emergency department. Further studies to be considered include investigating the benefit of starting HRS treatment in the emergency department as compared to the ward setting.

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Acknowledgments
None.

Conflict of Interest Statement & Funding
The author has no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea: WJT. Collect data/obtaining results: WJT. Write the manuscript: WJT. Critical revision of the manuscript: MT. Approval of the final version: MT. Administrative or technical advice: MT.

Cite as:
Tan WJ, Tiruchittampalam M. Hepatorenal Syndrome in the Emergency Department: A Case Report. Int J Med Students. 2014 Nov-2015 Mar;3(1):51-4.

Advanced Small Cell Lung Cancer with Cerebellar Metastases – A Case Report

Zhi Xiong Chong,[1] Nazmi M. Noori.[2]

Abstract

Background: Small cell lung cancer is an aggressive subtype of lung cancer whereby about one-third of cases are complicated with brain metastases. However, cerebellar metastases are uncommon and contribute to less than 10% of brain metastases. **Case:** We report a 76-year-old Malay male, an active smoker who presented with dyspnea and occasional cough with hemoptysis for one week. He also presented with headache and constitutional symptoms of malignancy. Clinical examination suggested the presence of right upper chest pathology and positive left cerebellar signs. His condition deteriorated two days later and he passed away after failed attempts at resuscitation. Chest radiograph showed right upper lobe collapse, and brain magnetic resonance imaging showed metastatic lesion in the left cerebellum extending to the right cerebellum. Post-mortem findings revealed small cell lung cancer with cerebellar metastases. **Conclusion:** Small cell lung cancer patients with brain metastases deteriorate very rapidly, and the management is mainly supportive. Primary prevention through education is the best way to reduce the incidence of lung cancer. In addition, secondary prevention and screening should be undertaken at earlier stages of the disease, as some studies have shown that combined chemotherapy and radiotherapy improve prognosis of malignancies detected at early stage.

Keywords: Lung Neoplasms, Small Cell Lung Carcinoma, Neoplasms Metastasis, Cerebellar Neoplasms (Source: MeSH, NLM).

Introduction

Lung cancer can be divided into two types, small cell (SCLC) and non-small cell carcinomas (NSCLC).[1] SCLC makes up about 20% of all lung cancer cases.[1,2] Compared to NSCLC, SCLC has a more aggressive disease course and almost always metastasizes to extra-thoracic organs.[2,3] 70% of patients with SCLC present with extra-thoracic metastases at the time of diagnosis.[3] Brain metastases are seen in 30.5% of patients with SCLC.[1,4] Cerebellar metastases are uncommon and contribute to less than 10% of brain metastases.[1,2,5]

Essentially, the prognosis of the SCLC patient with brain metastases is very poor with a median survival of one year.[3,5] One isolated study has reported survival of more than three years following intensive combination of high dose chemotherapy and radiotherapy.[3] In advanced cases, palliative care is as important as chemotherapy to improve the quality of life of the patient.[5]

We report an advanced case of SCLC with brain metastases, the management of which was mainly supportive. We would like to highlight the importance of primary and secondary prevention in the management of SCLC, as advanced disease carries a poor prognosis.[1,5]

Written informed consent was obtained from both the patient and his wife to discuss his case in the form of a published case report.

Key Points:

- SCLC with cerebellar metastases carries poor prognosis.
- The principle of management is mainly palliative than curative.
- Combined radiotherapy and chemotherapy helps to improve the survival rates.
- Primary prevention should be given more emphasis as prevention is better than cure.

The Case

This is a case of a 76-year-old Malay male farmer, an active smoker who started to smoke 50 years ago with a 40 pack-year history. He developed a non-productive cough six months prior to hospital admission. Two months later, he developed a headache, nausea, vomiting and loss of appetite. His original weight was 80 kilogram, of which he lost 15 kilogram (or 19% of his body weight). Initially, his daily activity remained normal. However, one month prior to admission, he developed difficulty in maintaining his balance while walking and became dependent on activities of daily living.

One week prior to admission, he started experiencing dyspnea and an exacerbation of his cough. On the day of admission, he developed hemoptysis and severe dyspnea, not relieved by rest. He was brought by family members to the hospital. On arrival, he was alert and was given oxygen support via nasal prong at 3L/minute. He had no symptoms of heart failure, chest pain, fever, history of tuberculosis contact, night sweating, history of prolong immobilization, calf pain or hematemesis.

The patient has underlying hypertension and hyperlipidemia diagnosed two years earlier and is on regular follow-up. His last follow-up was six months ago and he did not complain

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Submission: Sep 26, 2014
Acceptance: Jan 19, 2015
Publication: Feb 8, 2015
Process: Peer-reviewed

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of any problems to his primary care physician. Cardiovascular and respiratory examinations were normal during that visit. He is compliant with his medication (perindopril 2mg and atorvastatin 20mg daily). He has no family history of malignancy.

On physical examination, he was conscious, in pain and in respiratory distress. His blood pressure was 130/88mmHg. Respiratory examination revealed right upper lung pathology evidenced by reduced chest expansion and vesicular breath sounds. Bilateral supraclavicular lymph nodes were palpable. Cerebellar signs such as dysdiadochokinesia, positive finger nose test and heel shin test were present and predominantly affected the left side of his body. Examinations of other systems were unremarkable.

A series of investigations were completed. Arterial blood gas (ABG) demonstrated type I respiratory failure with Pa02 of 53mmHg. A full blood count and liver function tests were normal. Blood urea and serum electrolyte showed a slight elevation of serum urea and creatinine. The chest radiograph revealed a right upper lobe collapse with loss of pulmonary vascular markings (***Figure 1***). T2-weighted MRI displayed a single ill-defined hyperintense lesion measuring 6 x 5 cm in the left cerebellum extending to the right cerebellum (***Figure 2***). His electrocardiography (ECG) showed sinus rhythm and was normal. Tuberculosis work-ups, including a Mantoux test and sputum acid-fast bacilli were negative.

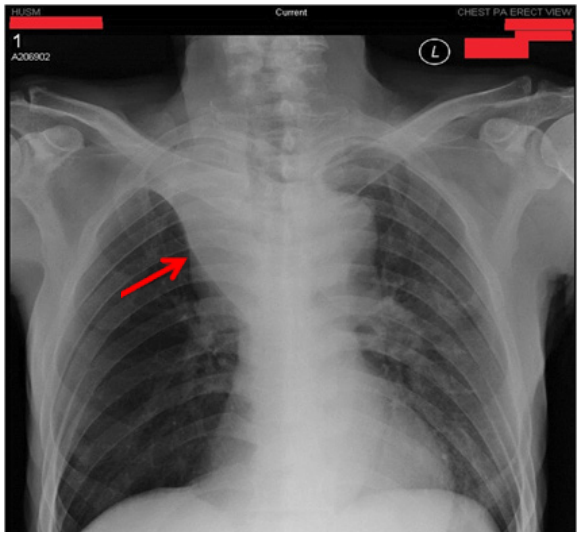
Bronchoscopy was performed and demonstrated the presence of a mass in the right main bronchus measuring 5 x 3 cm. Biopsy confirmed small cell lung cancer (SCLC) as the histological diagnosis (***Figure 3***). Computerized Tomography (CT) scan of the thorax was not completed, as the service was not available at that time. Based on the examination findings, bronchoscopy and MRI, he was diagnosed with stage IV (T2N3M1) SCLC with cerebellar metastases.

The possible differential diagnoses included pulmonary and cerebellar tuberculosis, pulmonary embolism, stroke and myocardial infarction. Tuberculosis is common in Malaysia, however he denied any night sweats, tuberculosis contact and tuberculosis work-ups were negative. Pulmonary embolism was possible, but he did not complain of pleuritic chest pain or have a history of immobilization. Stroke and myocardial infarction were possible based on his risk factors, such as male gender, old age, smoking, hypertension and hyperlipidemia, but the progressive onset of the disease made this unlikely. In addition, the ECG ruled out ischemic changes. Therefore, the most likely provisional diagnosis at this point was right lung cancer with cerebellar metastases.

He was admitted to the respiratory care unit and given oxygen support via oxygen mask at 9L/minute. He was also given intravenous morphine 10mg daily dose for pain relief and intravenous pantoprazole 20mg twice daily dose to prevent gastric ulcers.

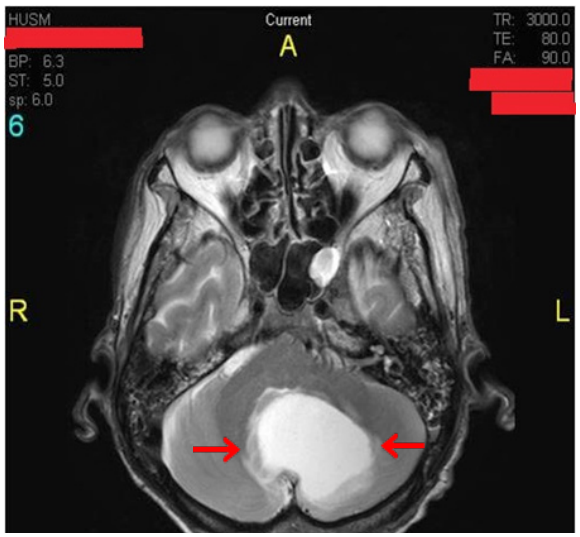
He was scheduled for palliative combined chemotherapy and radiotherapy. He was counseled on the disease burden and

Figure 1. Posterior-Anterior (PA) View Chest Radiograph.



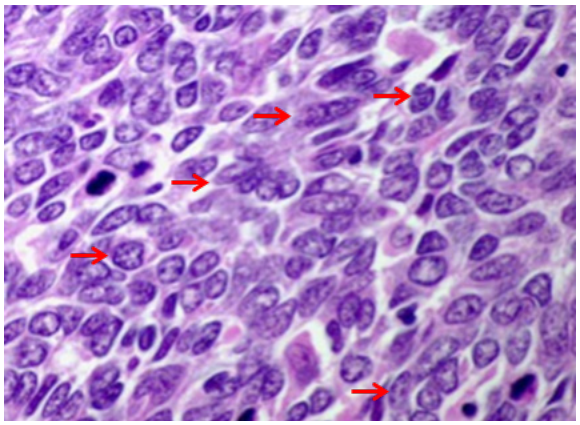
Legend: Figure 1 shows a right upper lobe collapse (red arrow) with loss of pulmonary vascular markings. The trachea also deviated towards the right side.

Figure 2. T2-weighted MRI of the Patient.



Legend: Figure 2 showes a single ill-defined hyperintense lesion (red arrows) measuring 6 x 5 cm in the left cerebellum extending to the right cerebellum. The lesion was surrounded by hypointense area suggestive of brain edema.

Figure 3. Higher Magnification of the Small Cell Lung Cancer Showing Numerous Mitotic Figures (red arrows).



the long term complications of the treatment. He understood and agreed to the treatment plan. The chemotherapy regimens included intravenous cisplatin 60-80mg/m2 on day 1 for every 28 days and intravenous etoposide 80-120mg/m2 on days 1 to 3 for every 28 days. Palliative low dose radiotherapy of about 20-30Gy was scheduled to be given in 5 to 10 fractions. Surgery was not indicated as the disease had already progressed to an advanced stage.

However, these therapies were not given because his condition rapidly deteriorated two days later. He collapsed suddenly, was intubated and given mechanical ventilation. Due to the sudden nature of his collapse, consent from the patient himself was not obtained for resuscitation. The decision to intubate was made after a discussion with family members. He was given intravenous adrenaline 1mg every five minutes. He passed away after failed cardio-pulmonary resuscitation (CPR) for 30 minutes. He was sent for post-mortem examination and autopsy confirmed that he had small cell lung carcinoma arising from right main bronchus with cerebellar metastases.

Discussion

The rapid progression of SCLC that has metastasized to the brain has been well documented in the literature.[1,5] Case reports report that patients may survive for three to five, after being treated with a combined chemotherapy and radiotherapy regimen.[2,3]

A systemic review and meta-analysis concluded that first line treatment for advanced SCLC should include four to six cycles of etoposide in addition to either cisplatin or carboplatin.[6] Oral or intravenous topotecan is recommended for patients that are resistant to first line treatments.[6] However, the routine use of thoracic irradiation in patients with metastatic SCLC is not recommended.[6] The optimal surveillance of metastatic disease involves 3-monthly CT scans to monitor disease progression and response to treatment.[6]

A randomized control study showed that thoracic radiotherapy in addition to prophylactic cranial irradiation improved survival rates in the thoracic radiotherapy group than in the control group.[7] However, Hirofumi Sakurai and et al., described two cases of SCLC with no metastatic lesions, where patients were started on early chemo radiotherapy and metastates were detected one and a half years later.[8] This draws a question as to whether early treatment will benefit the patient. Generally, most of literature still supports early detection and treatment to reduce morbidity and mortality.[1,2,5-7]

The majority of published case studies only discuss the benefit of early detection and treatment.[1,2,7] However, there is still a need for case reports which discuss a standardized management of advanced SCLC with brain metastases. Some case reports highlight the role of gamma knife surgery and intracranial irradiation in advanced disease to prolong the survival rate.[9,10] However, most patients do not easily accept brain surgery and irradiation because of concerns of intra-operative complications and post-operative intellectual reduction.[7] As for chemotherapy regimens, combination of cisplatin and etoposide are usually used although it still has limited proven efficacy in preventing metastatic disease.[7,8] All these factors contribute to the limited success rate in the treatment of advanced SCLC.[8]

Conclusion

In conclusion, the rapid progression of advanced SCLC has poses many difficulties to clinicians treating this cohort of patients. Although there is no definitive treatment for advanced SCLC, we would like to stress the benefits of prevention and early detection.[11,14] Attention should be drawn towards smoking as one of the most important contributors in the pathogenesis of lung cancer.[12,13] Primary prevention by education on smoking cessation should be implemented and enhanced in the healthcare system.[13-15] Images of lung cancer and obstetric complications caused by smoking have been printed on cigarette packing of many countries to discourage smoking.[14] A study has shown that public education on tobacco smoking is still very low and public education campaigns are needed urgently to raise the public awareness on the harmful effects of tobacco products.[16] Secondary prevention, which includes lung cancer screening among active and past smokers, should be encouraged for early disease detection.[13,17] Tertiary prevention has limited role in treating advanced lung cancer.[2,5] Therefore, prevention is always better than cure!

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Acknowledgments
We would like to express deepest gratitude to the patient, LMDZ, and his wife, MFM, for their willingness to participate in this case study.

Conflict of Interest Statement & Funding
The author has no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea: ZXC. Collect data/obtaining results: ZXC. Analysis and interpretation of data: ZXC. Write the manuscript: ZXC. Critical revision of the manuscript: NMN. Approval of the final version: NMN. Contribution of patients or study material: ZXC. Statistical advice: NMN. Administrative or technical advice: NMN.

Cite as:
Chong ZX, Noori NM. Advanced Small Cell Lung Cancer with Cerebellar Metastases – A Case Report. Int J Med Students. 2014 Nov-2015 Mar:3(1):55-8.

Acute Disseminated Melioidosis Presenting with Septic Arthritis and Diffuse Pulmonary Consolidation in an Otherwise Healthy Adult: A Case Report

Hai Sherng Lee,[1] Abdul Azeez Ahamed Riyaaz,[1] Seng Hong Yeoh.[1]

Abstract

Background: Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*. It is most prevalent in South-East Asia, northern Australia, and the Indian subcontinent. Septic arthritis is a rare manifestation of melioidosis. Melioidosis is usually found in patients with diabetes, heavy alcohol use, or chronic lung disease. **Case:** We report a case of melioidosis in an otherwise healthy 44-year-old male, who presented with acute painful left knee swelling, high-grade fever associated with chills, rigors and night sweats, and a productive cough. Examination revealed active synovitis with effusion involving his left knee, ankle and elbow joints and scattered crackles over both lung fields. Chest X-ray showed diffuse pulmonary consolidation. Abdominal ultrasound showed splenic micro-abscesses. The diagnosis was made based on a positive blood culture for *Burkholderia pseudomallei*. He was started on appropriate antibiotics and responded well, becoming afebrile after 48 hours, while his joint effusions disappeared after one week. **Conclusion:** Septic arthritis only occurs in 4% of patients with melioidosis. When there is diffuse pulmonary involvement, melioidosis may mimic disseminated tuberculosis, sepsis syndromes, and systemic vasculitis syndromes. This case is relevant for medical literature as melioidosis is emerging and is expanding its territories worldwide. It should be considered early in the differential diagnoses in endemic areas so that treatment can be started early to reduce its high mortality and morbidity.

Keywords: Abscess, Adult, Arthritis Infectious, Burkholderia pseudomallei, Melioidosis (Source: MeSH, NLM).

Introduction

Melioidosis is an infectious disease caused by the gram-negative saprophyte *Burkholderia pseudomallei*. It is most prevalent in South-East Asia, northern Australia, and the Indian subcontinent.[1] It is usually found in patients with diabetes, heavy alcohol use, or chronic lung disease.[1] The common manifestations are pneumonia (in half of all cases), genitourinary infection, skin infection, and bacteraemia without evident focus.[2] Complications include septic shock. Recurrent melioidosis is common unless long courses of treatment are given, and high mortality rates ranging from 14% to 40% have been reported despite optimal therapy.[1,2]

This case is unusual as the patient had none of the risk factors known to be associated with this infection and presented with septic arthritis, which is a rare presenting feature. It is an uncommon but important disease for clinicians to consider as its manifestations are protean, and it can mimic many diseases, including pulmonary tuberculosis.[1,2] Melioidosis should be considered as part of the differential diagnosis of patients with sepsis or abscesses in endemic regions. It is being recognized more frequently in these regions and is one of the important emerging infections that clinicians will encounter more in the future.[2,3] Informed written consent was obtained from the patient for writing and publishing this case report.

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Key Points:

- Melioidosis is endemic in tropical regions like South-East Asia and northern Australia and is usually found in patients with diabetes, heavy alcohol use, or chronic lung disease.
- Septic arthritis is a rare manifestation of melioidosis, found in only 4% of the cases at presentation.
- Mortality rates for melioidosis vary from 14% in Australia to 40% in northeast Thailand.
- The standard treatment for melioidosis comprises 10-14 days of intravenous ceftazidime or meropenem, followed by oral trimethoprim-sulfamethoxazole (TMP-SMX) plus doxycycline taken every 12 hours for 3 to 6 months.
- Melioidosis is becoming an emerging infection and expanding its territories worldwide. Due to its high mortality and morbidity, it should be considered early in the differential diagnoses of patients presenting with constitutional symptoms in endemic areas.

The Case

A 44-year-old male of Chinese ethnicity, who was previously healthy, presented to a district hospital in the state of Johor, Malaysia on July 28, 2014, complaining of a one-week history of acute onset painful swelling of his left knee. He had also developed a productive cough with scanty yellowish sputum, as well as high-grade fever associated with chills, rigors, and night sweats of similar duration. Three days before hospital admission, his left ankle and elbow joints were noted to be swollen and painful. He denied any recent trauma. Findings from a review of his cardiovascular, gastrointestinal, and genitourinary systems were normal. His past

Submission: Sep 30, 2014
Acceptance: Feb 23, 2015
Publication: Mar 30, 2015
Process: Peer-reviewed

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medical history was unremarkable, and there was no family history of autoimmune diseases. He denied any recent travel outside his state and contact with people with active pulmonary tuberculosis. He was a current smoker and had smoked around 16 cigarette pack-years since the age of 18. He drank alcohol only during social events and denied illicit drug use and high-risk sexual behaviours. He has worked as a tile layer for many years, during which he had occasional contact with the soil.

Examination revealed a man of average build, who appeared ill and mildly dyspnoeic. Upon admission, his vital signs included a pulse rate of 110 beats/min, a blood pressure of 110/61 mmHg, and a respiratory rate of 24 breaths/min. His temperature was 38.5 °C, and there were no pallor, icterus, lymphadenopathy, or skin rash noted. Respiratory examination revealed only scattered bilateral crackles while a mild hepatosplenomegaly was felt upon abdominal examination. His left knee, ankle, and elbow joints showed signs of active synovitis with effusion.

Investigations showed a white cell leukocytosis (22.2 x 10^9/L) with neutrophilia (86.4%) and deranged liver function tests [alanine transaminase (ALT): 56.2 U/L, aspartate aminotransferase (AST): 54.7 U/L, and alkaline phosphatase (ALP): 447.2 U/L]. Other investigations, including urine dipstick and renal profile, were normal. Chest X-ray showed bilateral diffuse patchy opacities suggestive of consolidation (***Figure 1***). An ultrasound of his abdomen confirmed mild hepatosplenomegaly and multiple irregular small hypo-dense lesions scattered in the spleen parenchyma, likely to represent micro-abscesses. At this point, a working diagnosis of septicaemia of unknown focus was made, and he was started on intravenous co-amoxiclav to cover the broad spectrum. Sputum samples were sent for acid-fast bacilli to rule out active pulmonary tuberculosis and came back negative. A human immunodeficiency virus (HIV) screening test was negative. He underwent aspiration of his left knee joint effusion, and a drainage catheter was inserted (***Figure 2***). The joint fluid was yellowish and clear, with no organisms detected on Gram's stain and culture.

On day two of hospital admission, his blood culture grew *Burkholderia pseudomallei*, leading to the diagnosis of disseminated melioidosis. He was started on intravenous ceftazidime 2 g three times daily and two tablets of oral co-trimaxazole 960 mg twice daily based on sensitivity results. He became afebrile after 48 hours, while his joint effusions disappeared over the first week of antibiotic treatment. The patient had to stay as an inpatient for two weeks for the intensive phase of intravenous antibiotic therapy, during which he did not develop any complications. A repeat chest X-ray done after two weeks of intensive antibiotic therapy showed marked radiological improvement (***Figure 3***). He was discharged home after two weeks, with a plan of continuation of oral co-trimaxazole for another 20 weeks and outpatient follow-up at 4-6 weeks intervals. Our patient believed that he acquired the infection at his workplace and was satisfied with the treatment he received. He understood the protracted nature of his illness and was committed to completing his prolonged antibiotic therapy.

Figure 1. Patient's Chest X-ray, Showing Bilateral Diffuse Patchy Opacities Suggestive of Consolidation.

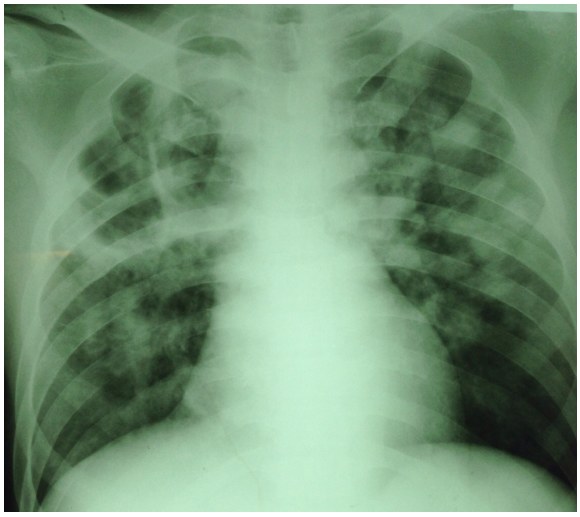


Figure 2. Patient's Left Knee with Effusion that had been Bandaged and Drained.

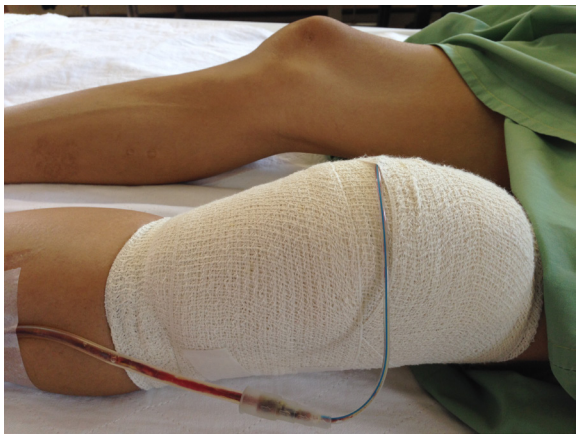
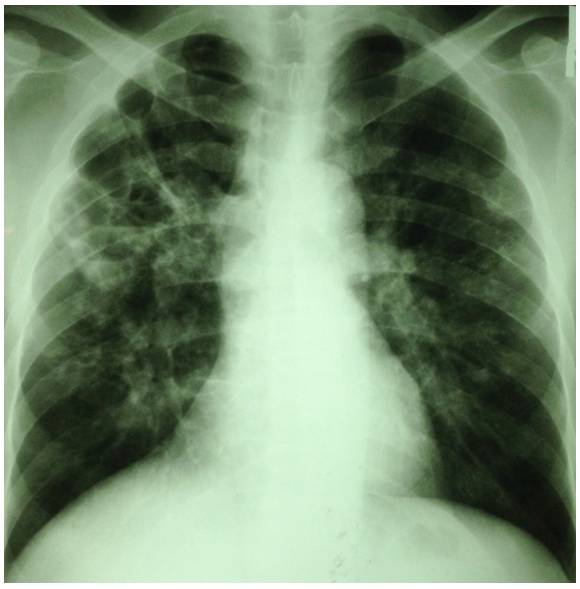


Figure 3. Patient's Repeat Chest X-ray After Two Weeks of Antibiotics, Showing Marked Radiological Improvement.



Discussion

Melioidosis is caused by the environmental Gram-negative soil saprophyte *B. pseudomallei*. Melioidosis is endemic in South-East Asia and northern Australia, with increasing recognition in the Indian subcontinent and elsewhere in the tropics. Northeast Thailand reports the highest number of cases, with an annual incidence of 50 cases per 100,000 people, making melioidosis the third most common cause of death due to infectious diseases in northeast Thailand.[1] In Darwin, tropical Australia, a 20-year prospective study from October 1989 yielded 540 cases of melioidosis.[2] Melioidosis has been studied extensively only in certain regions of Malaysia where there is known to be a higher incidence of disease. For instance, there were 44 new cases of melioidosis in the Malaysian state of Johor between January 1999 and December 2003.[4] Melioidosis is an emerging disease, as evidenced by increased reported incidence in endemic regions. For example, in Darwin, the prospective study identified 88 cases in the first five years, which increased steadily to 149 cases in the final five years.[2] In Northeast Thailand, there were 198 cases in 1997, which increased to 380 cases in 2006.[3] In addition, cases are being identified in new areas where melioidosis has not previously been reported.[1]

The primary modes of transmission of melioidosis are thought to be percutaneous inoculation in persons who are in regular contact with soil and water and, less commonly, via inhalation during severe stormy weather or by ingestion of contaminated food or water.[1] Melioidosis is predominantly seasonal, and more than 75% of cases occur during the rainy season. *B. pseudomallei* can invade macrophages and survive and replicate for extended periods of time. Phagocytes may be able to destroy the bacteria, but some bacteria can escape endocytic vacuoles and enter into the cytoplasmic space. They are also capable of infecting other cells through actin-based membrane protrusions.[1]

Melioidosis has a wide array of clinical signs and symptoms. It has an incubation period of 1-21 days, with a mean of 9 days, although prolonged periods of latency (up to 62 years) have been reported.[1] Its severity varies from an acute fulminant septic illness to a chronic infection, in which symptoms last for more than two months and may mimic malignancy or tuberculosis. In a descriptive study done over 20 years in tropical Australia, the most common presenting feature was pneumonia, which was present in 50% of cases, followed by genitourinary infection, skin infection, and bacteraemia without evident focus.[2] Septic arthritis, which was the principal presentation of our patient, and septic osteomyelitis are rare presenting features, with only 4% of cases having such manifestations. Over half of patients have bacteraemia on presentation, and septic shock develops in approximately one fifth. Internal-organ abscesses and secondary foci in the lungs, skin and soft tissues, bones and joints, or any other organ may occur. Up to 80% of patients with melioidosis have one or more risk factors for the disease, which include diabetes, heavy alcohol use, chronic pulmonary disease, chronic kidney disease, and thalassaemia. Glucocorticoid therapy and cancer were only associated in less than 5% of cases.[1-3] Our patient, however, had no such known risk factors.

The diagnosis of melioidosis is made from a positive culture for *B. pseudomallei* from any clinical sample, which in our patient's case was a positive blood culture. We would have faced diagnostic difficulties if the culture had been negative due to the non-availability of serological or genetic-based testing at the hospital where the patient was treated. But the delay in the identification of *B. pseudomallei* or misidentification as another species is not uncommon in laboratories that are unfamiliar with this organism.[5] A direct polymerase-chain-reaction assay of a clinical sample may be useful to provide a more rapid result than culture, but the assay is less sensitive, especially when performed on blood samples.[6] Serologic testing alone is not adequate to confirm the diagnosis, especially in endemic regions where background seropositivity is common.[7] The treatment of melioidosis includes prolonged courses of appropriate antibiotics due to the recalcitrant nature of the infection. An initial intensive phase should include at least 10 to 14 days of intravenous ceftazidime or meropenem followed by oral eradication therapy, which comprises trimethoprim-sulfamethoxazole (TMP-SMX) taken every 12 hours for 3 to 6 months, with or without doxycyline.[5] TMP-SMX plus doxycycline is considered the standard oral eradication regimen, although one recent study showed that TMP-SMX alone is not inferior to TMP-SMX with doxycycline.[8] Amoxicillin–clavulanate can be used as an alternative agent for eradication therapy when there are contraindications for the use of TMP-SMX.[9]

Mortality rates in melioidosis vary from region to region. For instance, it is approximately 40% in northeast Thailand,[5] but 14% in Australia.[2] Recurrent melioidosis occurs in approximately 1 in 16 patients, often in the first year after the initial presentation. Nearly 25% of recurrences are due to reinfection, with the remainder due to relapses from a persistent focus of infection.[10]

In conclusion, septic arthritis only occurs in 4% of patients presenting with melioidosis.[2] When there is diffuse pulmonary involvement, it may mimic disseminated tuberculosis, other acute disseminated or focal sepsis syndromes, and systemic vasculitis syndromes.[1,2] This case is relevant to the medical literature as melioidosis is becoming an emerging infection and expanding its territories worldwide. It should be considered early in the differential diagnoses of patients presenting with constitutional symptoms in areas where it is known to be endemic so that treatment can be started early to reduce its high mortality and morbidity.[2,3]

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Acknowledgments
We would like to thank the Department of Microbiology and Department of Radiology of Segamat Hospital for their assistance.

Conflict of Interest Statement & Funding
The author has no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea: HSL, AZAR. Collect data/obtaining results, Analysis and interpretation of data: HSL, SHY. Write the manuscript: HSL. Critical revision of the manuscript, Approval of the final version: AZAR.

Cite as:
Lee HS, Ahamed-Riyaaz AA, Yeoh SH. Acute Disseminated Melioidosis Presenting with Septic Arthritis and Diffuse Pulmonary Consolidation in an Otherwise Healthy Adult: A Case Report. Int J Med Students. 2014 Nov-2015 Mar;3(1):59-62.

A Medical Student Experience: Adding Value and Emotional Support to Patient Interactions

Dale S. DiSalvo.[1]

About the Author: *Dale DiSalvo is currently a third-year medical student at the Pennsylvania State University College of Medicine in Hershey, PA, USA out of a four-year medical school curriculum.*

The Experience

Note: Names have been changed.

Calvin was an older gentleman with chronic liver failure and ascites (fluid accumulation within the abdomen, specifically the peritoneal cavity), which recurred frequently despite medical therapy. I first met Calvin in a primary care practice and discussed the possibility of seeing him over the course of the year as part of a longitudinal patient care elective; he was agreeable to this.

A few weeks later, I called to check on Calvin after he had undergone a recent paracentesis. He seemed upset. It was not his first paracentesis; he typically had them done at the gastroenterology (GI) office. This time, however, the GI group was not available and instead he was offered an appointment with a different department at the main hospital. He got a little choked up on the phone, and excused himself.

The next time we met in person I asked about his paracentesis. The physicians at the main hospital were behind schedule, and all of the procedure suites were full. When he was taken for his procedure, he went to a makeshift procedure room with an unpadded table. Calvin typically had over 15 L of ascites drained per procedure, but they would not remove as much this time. When he asked why, the answer was "That's our policy".

After the procedure was over, his back was sore, and he still had quite a bit of ascites. Over the next two days, he continued to leak ascites from his puncture site. When asked about this, he started to tear up and admitted his fear of infection, ruining his furniture, or running out of bandages. He would rather live with the painful, tense ascites than ever have the procedure done there again.

Communication could have improved this experience for Calvin and it is the key for the attention of many other patients.[1] For example, a question to discover his preferences may sound like this: "We are running behind schedule. We've set up another room where you could have your paracentesis, but it's not very comfortable. Would you prefer to have your procedure now in that room, or would you rather wait for a regular procedure suite?" This would provide a sense of control. Providing a complete explanation for why they could not completely drain his ascites could have made him more understanding of the situation. For example, it may be important to mention the following: "We are short on nursing staff today, and there is no one to monitor you closely if you need medication after your procedure. Removing all of your fluid would mean you would need medication, so we can't remove it all today. It wouldn't be safe. Would you still like to have your paracentesis today?"

One survey found that patients view communication as the second most important competency of physicians, with diagnosis and treatment being most important.[2] Improving communication allows us to better identify our patients' concerns.[3] Furthermore, patient-centered care reduces the use of diagnostic tests.[4]

I was able to go with Calvin to his next paracentesis at the GI office. We made small talk while he waited. When the time came, as he was being taken back to the procedure room, he brought up his previous poor experience and his eyes started to tear up. I took his hand and reassured him that I knew the provider that was doing his procedure today, and she was wonderful. He looked at me and said, "You're the first person that ever called me at home to see how I did after one of these procedures." He took my hand and continued, "Sometimes I think you're the only one that actually listens."

How much of a difference can medical students make? On the day of Calvin's upsetting paracentesis, a medical student could have explained why things weren't running smoothly, why there were limitations on what they could do for him, and changed his entire experience. We can offer our time. A study of internal medicine interns showed that they spent only 12% of their time engaged in direct patient care activities.[5] Medical students have more time than that to spend with the patient. This is a privilege.

In a study involving patients that interacted with first and second year medical students in the ambulatory setting, 43% of

Submission: Dec 22, 2014
Acceptance: Feb 5, 2015
Publication: Feb 22, 2015

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patients felt that students added value to their visit.[6] We can do better than 43%, if we seek those opportunities out. If a preceptor is running behind in clinic and you as a student are seeing patients ahead of the preceptor, take that time to understand that patient's social issues. If things aren't running smoothly on rounds, and a patient seems frustrated, circle back and offer an explanation.

Take advantage of those opportunities, and carry those experiences forward throughout your training. I cannot imagine anyone discouraging a student from talking to a patient. It is my hope that medical students can aid in understanding our patients' concerns and build a more patient-centered healthcare environment.

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Acknowledgments
None.

Conflict of Interest Statement & Funding
The author has no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea, Write the manuscript, Critical revision of the manuscript, Approval of the final version: DDS.

Cite as:
DiSalvo DS. A Medical Student Experience: Adding Value and Emotional Support to Patient Interactions. Int J Med Students. 2014 Nov-2015 Mar;3(1):63-4.

The Meaning of "Do No Harm": A Medical Student Perspective

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About the Author: *Dale DiSalvo is currently a third-year medical student at the Pennsylvania State University College of Medicine in Hershey, PA, USA out of a four-year medical school curriculum.*

The Experience

The maxim, "First, do no harm" is strongly associated with the medical profession. It is a fundamental statement about the role of the physician in patient care. A patient should not be worse off after treatment than they were before. In modern medicine this can be a difficult standard to adhere to.

As a third year medical student with only one month of clinical experience, the surgical intensive care unit (SICU) was a daunting environment. I followed one patient for the duration of my rotation in the SICU who was a victim of a crush injury. It seemed that in some ways I knew everything there was to know about this gentleman. I knew all about his electrolytes, acid-base status, and liver enzymes. Yet on another level, I knew nothing about my patient. What was his life like? What were his values? For a time, I didn't even know his name… only his medical record number. One night as I lay in bed looking at the ceiling, I wondered if what we were doing could be considered harm.

A full complement of advanced technology was utilized to ensure his survival: mechanical ventilation, dialysis, tube feeding, surgical interventions and a long list of medications. What would he say if he could see himself in the SICU with a tube coming out of every orifice? All that I had learned in my first two years of medical school about history taking, patient communication, and open-ended questioning, did not prepare me for this experience. My patient was unconscious, and unable to share in the decision-making process. He had remained intubated and sedated since his emergency surgery on arrival.

I believe that if we cause unnecessary suffering, we have done harm. However, suffering is in the eye of the beholder and can be a complex concept. Cassel explores the problem of suffering in his article "The Nature of Suffering and the Goals of Medicine." He asserts that patients can suffer in physical and non-physical ways, and that physicians make an error by focusing primarily on physical suffering.1 Patients can suffer if they lose functional status, if they are no longer able to fulfill their roles or if they feel that they are a burden on their family. Furthermore, an individual in physical pain may not necessarily experience suffering.

For example, I read the story of a patient with breast cancer who believed that God had made her ill as punishment, as she had been unfaithful to her husband.2 It can be argued that this patient was not suffering from her symptoms as much as she was suffering emotionally, as her condition was complicated by feelings of guilt. Human beings are multifaceted and frequently we only peer into our patients' lives through one of those facets.

It was never possible for me to learn in what ways we may have been exacerbating or relieving my patient's suffering. The success of life support techniques seduces us into causing suffering for patients at times when they are at their most vulnerable. One study found that 75% of patients on a general internal medicine service would prefer to die at home, but of the patients in that study that died, 66% died in an institutional setting.3 There is room for improvement when it comes to doing no harm. One way to do this is to give patients the kind of death that they want, which will require a cultural change in medicine. We must acknowledge that death is the natural and inevitable conclusion of life, and not a failure of our profession.

For patients, like the gentleman I cared for in the SICU, that never get the opportunity to communicate their values and preferences regarding medical care, the solution is different. We must have the uncomfortable, but necessary conversations with our patients about what their values and preferences are if they were ever unable to speak for themselves while they are healthy. Preserving life does not necessarily mean that harm has been avoided. If a patient is condemned to a life of disability and chronic pain, is that harm? That is a matter of opinion. The most important opinion, that of the patient himself, was unfortunately unavailable. Sometimes our patients suffer because of our inability to accept death.

Submission: Feb 9, 2015
Acceptance: Feb 28, 2015
Publication: Mar 16, 2015

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Perhaps a husband would never want to live if he suffered a brain injury that would permanently alter his personality. For someone that watched a family member die waiting for a kidney transplant, perhaps they would never want to live a life dependent on dialysis. Perhaps a surgeon would never want to live without hands steady enough to operate. The only way to know is to ask the question.

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Acknowledgments
None.

Conflict of Interest Statement & Funding
The author has no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea, Write the manuscript, Critical revision of the manuscript, Approval of the final version: DDS.

Cite as:
DiSalvo DS. The Meaning of "Do No Harm": A Medical Student Perspective. Int J Med Students. 2014 Nov-2015 Mar;3(1):65-6.

Interviewing Dr Felipe Fregni: A Pathway to a Research Career

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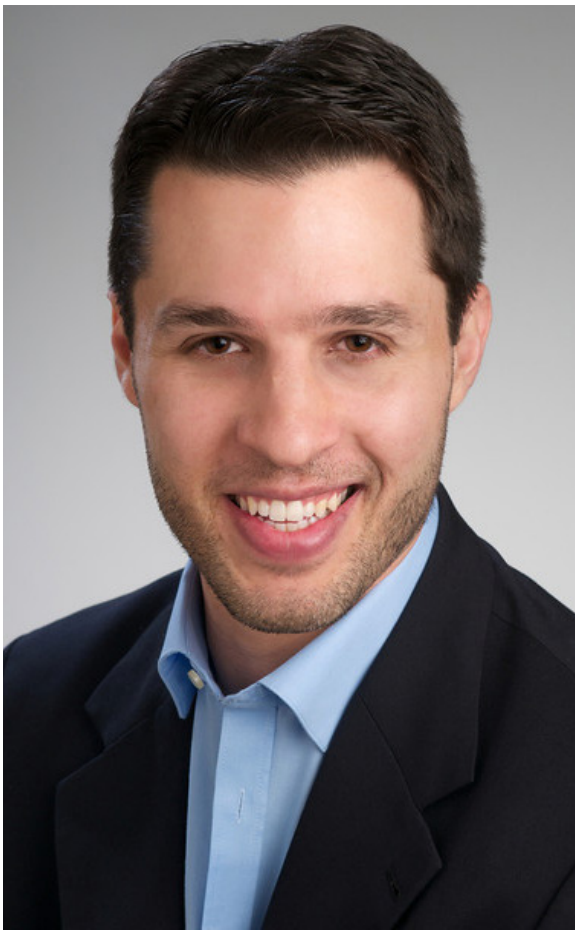
About the Author: *Juliana Bonilla Velez is one of the founders of the IJMS and a pupil of the Principles and Practice of Clinical Research course. As a visionary physician, she has served in a number of roles within the Association of Scientific Societies of Medical Students of Colombia (ASCEMCOL) and the International Federation of Medical Students Associations (IFMSA).*
Whitney Cordoba Grueso is the Youth Category winner of the 2014 "Afro-Colombian of the Year Award" and the former Director of Public Relations and Communications of IJMS. As a youth-empowerment leader, she has served in a number of roles within the ASCEMCOL and the IFMSA.

A talented Brazilian physician investigator, Felipe Fregni, is an Associate Professor of Physical Medicine & Rehabilitation and Neurology at Harvard Medical School, where he directs the Neuromodulation Laboratory at the Department of Physical Medicine & Rehabilitation at Spaulding Rehabilitation Hospital & Massachusetts General Hospital. He completed his medical studies, Neurology residency, and a Doctor of Philosophy (PhD) at the University of Sao Paulo and continued on to pursue postgraduate studies as well as a Master of Public Health (MPH) at Harvard Medical School. His philanthropic nature led him to design the Collaborative Learning in Clinical Research Program and the Principles and Practice of Clinical Research course with the Department of Continuing Education at Harvard Medical School to educate on basic and advanced training in clinical trials for physicians around the world.[1] As part of this course, he has reached to physicians and students of graduate and postgraduate studies in the medical field in 30 countries to offer a 9-month collaborative distance-learning course on clinical research. For this interview, he was invited to share his experiences and insight as a physician-scientist from Brazil with medical students worldwide.

Figure 1. Dr. Felipe Fregni.



1. Can you share with us a glimpse of your life history? Can you describe how your research career started?

I completed my medical school studies and residency at the University of Sao Paulo, Brazil. In the last months of my residency, I initiated my doctoral studies. The first time that I traveled to the United States was in 2000, where I completed an initial observership in the Department of Neurology at the Beth Israel Deaconess Medical Center (BIDMC) at Harvard Medical School. Here, I met the the Principal Investigator of the Laboratory of Brain Non-invasive Stimulation. Then, I went back to Brazil to finish my residency and continue my PhD studies. By the end of my PhD, I came back to Boston and started my post-doctorate fellowship.

When I came initially, I didn't know if I wanted to stay or not. I was open to opportunities. In my opinion, research is very important for you as a clinician. I knew that there are many limitations in the treatments we offer to patients and in order to understand and to provide better care, you need to understand science and research well. And this is where my motivation was to come to the USA, a place where there was more focus on research integrated in clinical practice.

I then started the Scholars in Clinical Science Program followed by my MPH in the Clinical Effectiveness program at Harvard

Submission: Feb 14, 2015
Acceptance: Mar 11, 2015
Publication: Mar 25, 2015

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School of Public Health. At this point, my research was going well; I was getting published and I was offered a position initially as Instructor and then as Assistant Professor of Neurology. Then, I was faced with the decision about whether I wanted to go back to more clinical work or stay more centered in research, and I chose to stay more dedicated to research and teaching. At this point, I was then recruited to Spaulding Rehabilitation Hospital where I have my own laboratory to continue my projects. And now I do most of my time in research

2. What were your thoughts and professional goals when you were a medical student?

As a medical student, what you are most focused on is figuring out in what you want to do your residency, and I was very open to specialties. One of my last rotations was neurology and I realized I really liked it. At this stage, I was focused on what my next step was going to be and that was residency so that was my main concern. I had thought about research and I knew I liked research. As a medical student, I was very critical of what I heard from my professors and if there was evidence to support our decisions, I was always questioning. I wouldn't imagine that when I graduated so many years ago that I would be here now and doing what I do now. I think you should be open to opportunities.

3. Was there a defining moment when things changed?

I think it was more a process. I had ideas in my head and there were issues in clinical practice that I wasn't happy and I didn't know how to resolve these issues- issues that kept me thinking. Then I thought that if I went through a research career and if I understood more and by doing that I would become even more passionate about Neurology. So I think it was a process, it took me since finishing medical school about 5-6 years to see that this was really what I wanted to do. I saw that this made sense in terms of what I believed in. I was never satisfied with current knowledge in medicine and the simplistic model for diseases and I wanted to do something different, to propose a change, and this would only be possible through research and producing new knowledge.

In my first year of medical school, before there was Internet, I came across a book in our medical school's library written by an editor of the New Scientist Journal, and I can never remember the actual name nor have I been able to find it, but it was called something like "The Magic Bullet" saying that there are so many limitations with drugs and that we don't fully understand what they're really about and then discusses the limitations of our knowledge. This helped me appreciate Medicine with different eyes. I think everything happens for a reason.

4.What was the process for you to arrive to your current line of research?

It was a couple of things. When I was doing my observership at BIDMC, I was with a group of students and one of them told me he was working in a laboratory that worked on brain stimulation and I thought that was very cool so I went to see it. For me it made a perfect match. It was a technique that could study brain plasticity, how the brain changes according to disease and behavioral stimulation and based on that it went across different conditions like stroke and Parkinson's disease, which gave me the opportunity to keep working on different conditions focused on learning more about how diseases change neuroplasticity and how these changes are locked. It was a great field for learning more in general as opposed to focusing on a very specific question, which was more what I wanted to do, something that would transcend, seeing a bigger picture

5. What is the contribution of your area of research to healthcare and answering the health problems that we face? What are the biggest challenges?

I think the main thing that we are showing is how the brain changes with diseases and that is important. Your brain changes because you have a lot of neurotransmitters released in response to disease or to a lesion, for example in stroke, but it also changes trying to adapt, trying to compensate for what has happened. So we're showing that, and showing that if you try to block or reverse some of these changes you can induce therapeutic effects. So this is a great contribution to clinical care. We're showing with quantitative methods that its not only disease but what we call maladaptive plasticity that has an effect on the brain. And in stroke we're showing that if you go not to the side of the lesion but to the contralateral side you can induce an improvement as well. We have also seen that if you have a lesion it can cause an excitability of the areas that cause chronic pain, and then the brain becomes more sensitive to stimulus in pain-related centers. So these are some of the contributions we are giving to medicine.

6. In your opinion, what is the future of research in Neurology?

It's a difficult question. I think research should be more balanced in terms of basic science and clinical so it can have more translation. For example, I gave a presentation on the PPCR course showing how we spend millions of dollars to develop interventions for acute stroke, from ten that showed great results in animals only one of them showed a significant result in humans in a small phase II trial and when it went to phase III trial it showed no changes. So, I think it is important to have more effort placed on translation. Another area that would help develop the field is finding better biomarkers for neurological diseases. There are no biomarkers for pain or stroke; there are some that can be used but they're not very reliable for Parkinson's disease and Alzheimer's disease, and you can see clinical outcomes - which is fine- but we don't have biomarkers as you have for other diseases like enzymes in myocardial injury.

In PMNR the great challenges are in terms of testing because most interventions are based on physical, occupational, and speech therapy more than pharmacological therapies, and these haven't been tested systematically. By studying them better it can help us understand which patients respond better to which treatments. So having more large open label studies would be interesting as well.

7. What has been the greatest accomplishment in your career?

It's difficult to say, but for example for me some great accomplishments are having my own laboratory and mentoring stu-

dents, as well as becoming faculty here. But one thing I think is a great accomplishment and I am very passionate about is the clinical research course because I think it is the only way you can have a system changed is though spreading knowledge. I think it would be a combination of these things. And also the research findings we've already discussed.

8. How have you contributed to the advancement of clinical research in developing countries?

This for me is very important. I've contributed in two ways. The mission is to improve clinical practice and to improve the level of clinical care because we can not just do all things ourselves so we need to try to help in areas where there's more need. There are different ways to help: one of them is the clinical research course, which was designed to be an international course with colleagues in Brazil and it has now reached many countries. Another one has been pursuing collaborations with some of the laboratories in developing countries. I know they face difficulties doing research at different levels, for example getting the equipment, so through our collaboration we've been able to do great projects together.

10. What advice would you give medical students who are interested in getting involved in research?

I think as medical students you need to be a bit lucky and be in a good school with good mentors and be more critical. What's most important is that you should choose your mentor and not only the mentor that is available to you, and that sometimes is hard to do. This is a match that serves both ways. I don't think in medical school the topic is as important – what to research in – but I think its more about who you choose to work with because then you learn what research is about; you learn the methods.

9. What advice do you have for medical students worldwide?

In the context of evidence-based medicine, I'd say be curious and critical of what you learn. Don't just do research because it improves your CV; understanding research can lead you to do better clinical medicine and then look for someone who can really help you achieve that. And for future clinical investigators, you need to devote time and dedication to really learn well because it will take more than just 6 months of doing research. Working hard, you need 3 to 4 years to be able to then be independent in research.

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Acknowledgments
The authors of this Interview would like to thank Dr. Felipe Fregni for his valuable time and also for sharing his research experience with the medical students worldwide.

Conflict of Interest Statement & Funding
The authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions
Conception and design the work/idea, Collect data/obtaining results: JBV. Analysis and interpretation of data, Write the manuscript, Critical revision of the manuscript, Approval of the final version: JBV, WSCG.

Cite as: Bonilla-Velez J, Cordoba-Grueso WS. Interviewing Dr Felipe Fregni: A Pathway to a Research Career. Int J Med Students. 2014 Nov-2015 Mar;3(1):67-9.

Challenges Faced by International Medical Students Due to Changes in Canadian Entrance Exam Policy

To the Editor,

About the Author: *Pishoy is currently a final year medical student at the National University of Ireland. He is also the past Chairperson of the Association of Medical Students in Ireland and the Vice-President of the North American Irish Medical Student Association. He is also a recipient of the Alberta Innovates-Health Solutions Summer Studentship and the Canadian Institutes of Health Research Summer Student Research Award.*

The process of applying to postgraduate training in Canada is an arduous procedure; however, it ensures that trainees are of the highest caliber and capable of delivering an excellent standard of care. International medical school graduates must complete a postgraduate training program in order to practice as independent physicians. The application process begins with candidates undertaking the Medical Council of Canada Evaluating Examination (MCCEE), a four-hour clinical knowledge multiple choice exam that covers a wide spectrum of disciplines including medicine, surgery, obstetrics and gynaecology, psychiatry, paediatrics, and public health. Previously, this was the only examination required by most postgraduate training programs in order to apply. The MCCEE is offered in five different sittings that are evenly spaced throughout the year (Available from: http://mcc.ca/examinations/mccee/; cited 2014 Dec 1.)

The 2015 application cycle marks the first year in which most postgraduate programs will also require the completion of a second examination, the National Assessment Collaboration (NAC) OSCE. The NAC OSCE is a clinical skills exam covering the same disciplines as the MCCEE and may only be undertaken after the successful completion of the MCCEE. The NAC OSCE is offered twice a year: in September and March. Students wishing to apply to postgraduate training, which is organized by the Canadian Resident Matching Service (CaRMS), must submit their examination results for both of these exams by the November of the application year.

In order to facilitate this new examination, the Medical Council of Canada has made changes to the MCCEE eligibility, which now allows international medical students to take the exam earlier, 20 months prior to graduation (Available from: http://mcc.ca/2013/03/mccee-eligibility-changes-for-international-medical-students/; cited 2014 Dec 1.) For prospective applicants, this requires them to take the MCCEE earlier than previous cohorts of applicants. Previously, students would undertake the MCCEE in September of the final year of medical school. In contrast, students are now recommended to undertake the MCCEE in March of their penultimate year and undertake the NAC OSCE in September of their final year (Available from: http://mcc.ca/examinations/nac-overview/application-information/#Timing; cited 2014 Dec 1.)

This new timeline was intended to assist international medical students in the application process, providing them the opportunity to write both the MCCEE and NAC OSCE prior to the CaRMS deadline. However, this new timeline poses several dilemmas. The first is the considerable increased workload placed on international medical students during the academic year. They are now obligated to study for the MCCEE and NAC OSCE on top of their clinical workload, often having to cover topics that they have yet to cover in their local curriculum to prepare for the examinations. As a result, the authors speculate that these changes may result in lower scores on the MCCEE, in addition to lowering their clinical performance at their home institutions.

Submission: Nov 11, 2014
Acceptance: Dec 14, 2014
Publication: Dec 31, 2014

Furthermore, the timing of examination is not student-friendly. The only NAC OSCE sitting for which student applicants are eligible is scheduled just a few weeks into the academic session (mid/late September) of their final year. We therefore recommend that the NAC OSCE be offered at more frequent intervals during the year, with at least one summer sitting. For some students, this provides the opportunity to study for, and complete, these Canadian exams during their summer break, alleviating the need to be excused from even more clinical activities.

Even in the event that a motivated student can complete all these examinations, in some provinces they are still not eligible to apply to postgraduate training programs. For example, Alberta requires applicants to graduate in the December prior to the anticipated start date of residency, automatically disqualifying most medical students (with the exception of Australian medical student who graduate in December). This is in place to ensure that graduates can participate in a mandatory induction program (Available from: http://www.aimg.ca/index.php?page=64; cited 2014 Dec 13.) However, by scheduling the induction program in June and requiring proof of graduation by the end of May, programs can avoid the automatic exclusion of students wishing to start training immediately after they graduate. Quebec finds itself in a similar situation, requiring that candidates successfully complete a third examination, the Medical Council of Canada Qualifying Examination Part 1, which is not possible for students to write before the CaRMS deadline for applications (Available from http://www.cmq.org/en/ObtenirPermis/DiplomesInternationaux; cited 2014 Dec 13.) What this means for Alberta, Quebec, and other provinces with similar requirements, is that they are forgoing the opportunity to hire some of the brightest students who are taking up positions in other provinces because they do not wish to wait a year following graduation to start their postgraduate training.

While these examinations are necessary to protect medical standards and the quality of healthcare, these unnecessary hardships can be avoided by allowing international medical students to simultaneously register for both the NAC OSCE and MCCEE, without requiring them to be done in a specific order, similar to the United States Medical Licensing Examination system (Available from: http://www.usmle.org/bulletin/eligibility/; cited 2014 Dec 1.) These proposed solutions would provide students with the opportunity to study and write these examinations without compromising their education at their local institutions.

In conclusion, the new changes in MCCEE eligibility have permitted international medical students to apply for postgraduate training in Canada within the CaRMS application timeframe. However, slightly modifying the examination timeline would improve the process further and lighten the academic hardships placed on student applicants.

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Acknowledgments: None.

Conflict of Interest Statement & Funding: The Author has no funding, financial relationships or conflicts of interest to disclose.

Author Contributions: Conception and design the work/idea, Write the manuscript, Critical revision of the manuscript, Approval of the final version: PG, SF, JG.

Cite as: Gouda P, Fanous S, Gouda J. Challenges Faced by International Medical Students Due to Changes in Canadian Entrance Exam Policy. Int J Med Students. 2014 Nov-2015 Mar;3(1):70-1.

Grains of Sand and an Artist's Hands

To the Editor,

It is with great pride that I write this Letter to the Editor on behalf of Ms. Shelly Mingqian Xie, our second-year medical student at the University of Texas Southwestern Medical School, whose work has been featured this year by your journal.

Shelly is a unique individual who has an extraordinary gift for the arts in all forms, along with a deep understanding of the human condition and how disease impacts individuals, families, and society at large. She has the ability to combine her artistic gifts with her love of science to make a powerful and significant impact on health.

Coming to the U.S. at the age of 12, it did not take long for Shelly to excel academically and discover her gifts for drawing and painting. While serving as a hospital volunteer during high school, she began a program painting portraits of patients during emotionally difficult times, such as a mother holding a stillborn baby or a dying young man. Through these experiences and the conversations she had with patients as she drew their portraits, Shelly developed a greater understanding of the impact of disease, illness, loss and death; the importance of communication, empathy and compassion; and the resilience of the human spirit despite devastating circumstances. This first important step of combining her art with science planted the seed that led to her pursuit of medicine as a future physician.

After researching Schistosomiasis during her undergraduate years at Stanford, she had another opportunity to combine art, the humanities, and science. Her new understanding of the devastating global impact of this preventable and treatable disease inspired her to self-learn a new 3D art media – sand art – to tell the story of families impacted by Schistosomiasis, and later Chagas and hookworm disease.

It did not take long for national and international organizations to appreciate the powerful impact this art form, combined with storytelling through live or recorded demonstrations, could have on neglected tropical diseases. Even during her medical school coursework here at UT Southwestern Medical Center, Shelly has presented her work at national and international conferences to promote education, public health interventions, and treatment to improve the health of families impacted by these diseases. Very few medical students have had such a worldwide impact on health and health promotion at such an early stage in their careers.

After having the great pleasure of getting to know her well as a person, it is clear that there are few students as humble, truly empathetic, and sincere as Shelly Xie. Her life experiences, appreciation for diverse cultures, experiences getting to know hundreds of patients and their struggles, and incredible natural gifts in the visual arts and creative writing, along with the passion to serve and improve the health of others, provide her an incredibly unique opportunity to make a significant impact. We could not be prouder as an institution of her work, her gifts, and the caring, compassionate future physician she is becoming. It is hard to predict where these talents will take her as she matures in her medical education, but we are all incredibly excited to support her endeavors and celebrate the impact she will have on improving lives in our global community.

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Submission: Mar 9, 2015
Acceptance: Mar 9, 2015
Publication: Mar 15, 2015

Acknowledgments: None.

Conflict of Interest Statement & Funding: The Author has no funding, financial relationships or conflicts of interest to disclose.

Author Contributions: Write the manuscript, Approval of the final version: APM.

Cite as: Mihalic AP. Grains of Sand and an Artist's Hands. Int J Med Students. 2014 Nov-2015 Mar;3(1):72.

Response to Medical Students' Attitudes towards Female Sex Workers

To the Editor,

The article by Nakagawa and Akpinar-Elci on medical students' knowledge and attitudes toward female sex workers and their occupational risk factors left us with ambiguous reflections.[1] The crux of this study raises an important issue: sex work, sexual abuse toward women, and sexually transmitted diseases (STDs) are big problems and should be widely discussed in the medical environment. It is essential to provide care to female sex workers through educating medical students and young doctors, regardless of their religious and upbringing influences. It is, however, important to understand cultural and regional differences in the perception of prostitution due to the ubiquitousness of this issue in different parts of world. We strongly agree with Nakagawa and Akpinar-Elci's statement on the importance of providing care to female sex workers as a vulnerable group.

However, the paper seems to be misleading due to several problems with the group size and selection, as well as with the presentation of the data. The distribution of 292 students across 56 countries does not reflect the distribution of medical students in the world.[2] Students from five countries (United States, Italy, Iran, Brazil, and a country wrongly identified as Italy with a line extending to the island of Sicily) made up 52.1% of the study sample, while in forty-two of the countries studied, only three or less students (1% of the total study sample or less) participated in the online survey. This is not a representative sample of the world population of medical students, an issue which could undermine the validity of the study results.[3-4] In addition, Figure 1 shown in the Nakagawa and Akpinar-Elci paper presents misleading data. Italy is marked twice (10.3%, n=30 and 5.8%, n=17), and this information is not consistent with the given text. Three countries are mentioned in the article and only two of them are correctly represented in the figure. A complete table providing the country demographics (student distribution and their responses) published as an appendix would be a valuable addition to the manuscript.

In addition to errors in the first figure, the statistical analysis is not sufficiently described in the text. There are neither exact results of the mentioned two-sample t-tests nor measured attitudes. Furthermore, the stratification of the data seems to be insufficient; there is no detailed information about the educational background of sampled individuals. The students should be divided into additional groups, for example, according to the Gross Domestic Product (GDP) per capita or to their religion. Every religion has different attitudes towards prostitution, which was not considered in the results.[5] Furthermore, the legality of prostitution in specific countries is not clearly identified. Many countries do not have regulated laws about the sex industry.[6] All of this may lead to erroneous conclusions and misunderstanding.

In conclusion, the study by Nakagawa and Akpinar-Elci contributed a great deal to the understanding of the problems faced by female sex workers. There are, however, several components of the study design that are important to bring to the attention of readers to facilitate a more comprehensive discussion on this topic. We believe that this paper will definitely prove to be an eminent study of this subject.

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Acknowledgments: None.

Conflict of Interest Statement & Funding: The Author has no funding, financial relationships or conflicts of interest to disclose.

Author Contributions: Conception and design the work/idea, Analysis and interpretation of data, Write the manuscript: HG, JW. Critical revision of the manuscript: JW. Approval of the final version: HG.

Cite as: Garnier H, Wisniewski J. Response to Medical Students' Attitudes towards Female Sex Workers. Int J Med Students. 2014 Nov-2015 Mar;3(1):73.

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Submission: Jan 18, 2015
Acceptance: Feb 28, 2015
Publication: Mar 24, 2015

Reply to Letter to the Editor, "Response to Medical Students' Attitudes towards Female Sex Workers"

To the Editor,

We would like to first extend our gratitude to the authors of the letter to the editor in the interest of our article, "Medical students' knowledge and attitudes toward female sex workers and their occupational risk factors".[1,2] By discussing the meaning of our study results and limitations, we raise the potential for future research to clarify medical student attitudes toward female sex workers and the factors that influence such attitudes. We agree with the letter-writers that this topic must be explored further, with special attention to the cultural and regional differences in the perception of sex work.

Considering the small sample size and the selection and participation biases, we agree that our study sample does not reflect the world's population of medical students. We want to thank the letter-writers for bringing to our attention the misrepresentation of student participation on the world map. On the map, the line that should have pointed to Malta (5.8% of the study sample, n=17) was extended to the island of Sicily in error. A revised version of this map is shown in ***Figure 1***. Furthermore, additional information about each participating country's student demographics can be found in ***Table 1***.

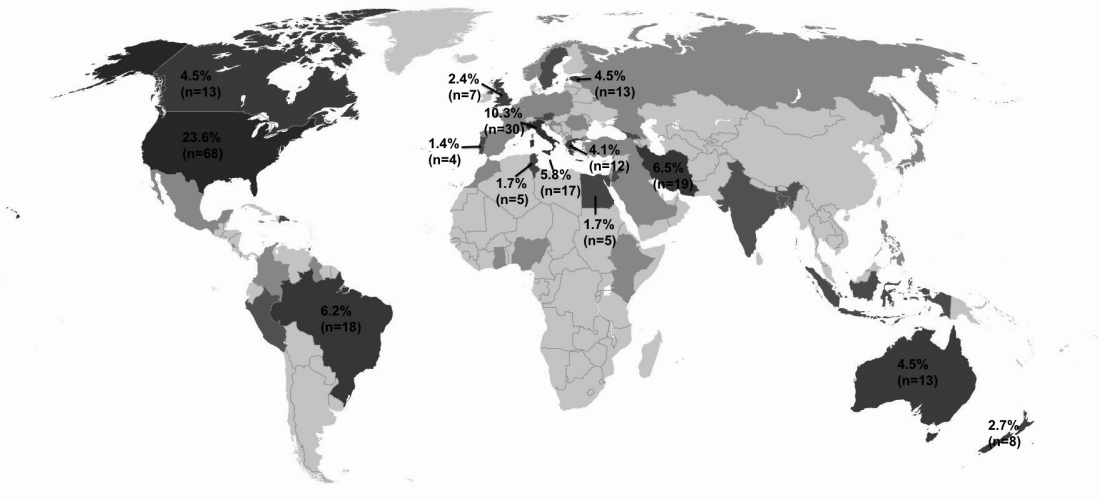
While we cannot generalize medical students' attitudes on a global scale, we believe our study did raise interesting questions about factors outside of formal education/training that influence attitudes. Although our student sample represented a variety of prior educational experiences and graduate degrees, stratification of student data based on educational background showed no statistically significant variations in attitude or knowledge scores. Exact results of the two-sample T-tests for differences in mean attitude and knowledge scores among different groups, as well as differences in their educational backgrounds, can be found in ***Table 2*** and ***Table 3***. Other factors which could be more influential to medical student attitudes toward sex workers, such as socioeconomic, religious, and cultural determinants, remain to be explored.

Following the suggestion to stratify students by country GDP per capita, we found GDP per capita was positively correlated with both country mean attitude scores (r=0.36, p=0.007) and mean knowledge scores (r=0.28, p=0.04) (Country GDP obtained from World Bank 2013 data: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD, updated 2015; cited 2015 Mar 21). However, these are loose correlations for our limited study sample. To effectively explore the relationship between country economic status and attitudes toward sex workers, several factors may be taken into account, including but not limited to: the impact of economic status on investments in education, medical training and the health care system itself; the relationship between national economic growth and public access to health care; and the influence of economic status on the size of the informal job sector (World Health Organization. The World Health Report 2000: Health Systems, Improving Performance. 2000. Available at: http://apps.who.int/iris/bitstream/10665/42281/1/WHR_2000.pdf?ua=1, cited 2015 Mar 21).[3-6]

In agreement with the letter-writers' opinion, different religions undoubtedly guide different attitudes toward sex work. We chose not to ask students with which religion they identify in particular in order to survey demographics more broadly. Now seeing a potential relationship between "religiousness" and attitudes toward sex workers, it is important to explore in detail what students mean when they self-identify as religious or not religious and what influence different religious teachings might have on attitudes toward sex workers.

It is true that many countries have ill-defined and unregulated laws controlling the sex industry. Sources such as the U.S. Department of State Country Reports on Human Rights Practices, which provides data to the Joint United Nations Programme on HIV/AIDS (UNAIDS) and other international agencies, reveal inconsistencies between the legality of prostitution and regulation of its context. In the UK, for example, prostitution is legal, but the organization of brothels for prostitution is illegal. In Iran, prostitution is illegal, but occurs under the legal allowance of sigheh, a temporary marriage (2009 Country Reports on Human Rights Practices. Available at: http://www.state.gov/j/drl/rls/hrrpt/2009/index.htm, cited 2015 Mar 21). In addition to vague laws and different forms of sex

Figure 1. Percentages of Participants from the Top 14 Most Represented Countries.



Legend: Other 42 participating countries contained three participants (1%) or less of the total study sample (n=292)

Submission: Mar 23, 2015
Acceptance: Mar 25, 2015
Publication: Mar 25, 2015

Table 1. Participating Countries' Demographics, Mean Attitude Scores, and Mean Knowledge Scores.[†]

Home country (No. participating students)	Mean age[‡]	Mean No. completed terms in medical school[‡]	Previous education/ training in occupational health/social determinants of health (%)	Sex		Self-identified religiousness		Prostitution in country of intended practice		Mean attitude score	Mean knowledge score (% correct responses)
				Male (%)	Female (%)	Religious (%)	Non-religious (%)	Legal (%)	Illegal (%)		
Australia (n=13)	23	4	46.2	53.8	46.2	7.7	76.9	100.0	0.0	34.7	96.2
Austria (n=3)	25	8	33.3	100.0	0.0	0.0	100.0	100.0	0.0	35.7	97.9
Bahrain (n=1)[†]	22	10	100.0	100.0	0.0	100.0	0.0	0.0	100.0	34.0	78.6
Bangladesh (n=2)	24	3	100.0	50.0	50.0	100.0	0.0	0.0	50.0	26.0	91.2
Belgium (n=1)[†]	23	4	100.0	0.0	100.0	0.0	100.0	100.0	0.0	34.0	94.1
Brazil (n=18)	23	4	66.7	38.9	61.1	61.1	33.3	94.4	5.6	29.8	87.7
Canada (n=13)	24	4	61.5	46.2	53.8	23.1	76.9	84.6	15.4	32.6	99.1
Colombia (n=1)[†]	24	10	100.0	0.0	100.0	100.0	0.0	100.0	0.0	33.0	93.8
Croatia (n=1)[†]	24	12	0.0	100.0	0.0	0.0	100.0	0.0	100.0	29.0	93.3
Czech Republic (n=1)[†]	22	6	0.0	0.0	100.0	0.0	100.0	100.0	0.0	30.0	94.1
Dominican Republic (n=3)	26	12	33.3	33.3	66.7	100.0	0.0	66.7	33.3	29.0	84.1
Egypt (n=5)	22	6	80.0	60.0	40.0	60.0	0.0	0.0	80.0	27.0	87.2
Estonia (n=13)	21	4	23.1	7.7	92.3	0.0	100.0	92.3	0.0	31.9	89.4
Ethiopia (n=1)[†]	21	9	100.0	0.0	100.0	0.0	100.0	100.0	0.0	27.0	100.0
France (n=1)[†]	20	6	0.0	0.0	100.0	0.0	100.0	100.0	0.0	ŧ	93.3
Georgia (n=3)	23	2	0.0	33.3	66.7	100.0	0.0	66.7	33.3	25.3	86.8
Germany (n=1)[†]	27	9	0.0	0.0	100.0	0.0	100.0	100.0	0.0	33.0	100.0
Ghana (n=1)[†]	21	6	0.0	100.0	0.0	100.0	0.0	0.0	100.0	31.0	100.0
Greece (n=12)	23	4	33.3	41.7	50.0	16.7	83.3	91.7	0.0	31.3	88.3
Grenada (n=2)	20	3	50.0	50.0	50.0	50.0	50.0	0.0	100.0	29.0	96.9
Guyana (n=1)[†]	25	10	100.0	0.0	100.0	100.0	0.0	0.0	100.0	23.0	100.0
India (n=2)	24	11	0.0	50.0	50.0	50.0	0.0	100.0	0.0	35.5	96.7
Indonesia (n=3)	21	8	66.7	33.3	33.3	100.0	0.0	33.3	66.7	25.0	94.1
Iran (n=19)	24	8	21.1	52.6	47.4	63.2	31.6	0.0	100.0	29.1	88.0
Iraq (n=1)[†]	21	0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	25.0	92.9
Israel (n=1)[†]	34	4	0.0	0.0	100.0	0.0	100.0	100.0	0.0	28.0	100.0
Italy (n=30)	22	5	65.0	30.0	70.0	53.3	40.0	90.0	0.0	30.5	87.4
Jamaica (n=1)[†]	25	9	100.0	0.0	100.0	100.0	0.0	0.0	100.0	33.0	88.2
Japan (n=1)[†]	21	5	0.0	0.0	100.0	0.0	100.0	0.0	100.0	26.0	91.7
Jordan (n=3)	21	8	33.3	100.0	0.0	0.0	66.7	0.0	100.0	23.7	97.8
Kenya (n=1)[†]	21	2	0.0	100.0	0.0	0.0	100.0	0.0	100.0	32.0	93.3
Lebanon (n=1)[†]	25	16	100.0	100.0	0.0	100.0	0.0	0.0	100.0	37.0	94.1
Macedonia (n=1)[†]	29	16	100.0	0.0	100.0	0.0	100.0	100.0	0.0	29.0	100.0
Malta (n=17)	20	4	11.8	35.3	64.7	64.7	29.4	5.9	88.2	29.2	96.7
Mexico (n=1)[†]	23	10	0.0	100.0	0.0	100.0	0.0	100.0	0.0	34.0	76.5
Morocco (n=1)[†]	21	8	0.0	0.0	100.0	100.0	0.0	0.0	100.0	31.0	88.9
Netherlands (n=1)[†]	23	3	100.0	0.0	100.0	0.0	100.0	100.0	0.0	39.0	93.3
New Zealand (n=8)	22	5	50.0	25.0	75.0	37.5	62.5	100.0	0.0	33.3	99.2
Nigeria (n=1)[†]	25	0	0.0	0.0	100.0	100.0	0.0	0.0	100.0	31.0	100.0
Norway (n=1)[†]	23	7	0.0	0.0	100.0	0.0	100.0	100.0	0.0	33.0	100.0
Peru (n=2)	20	7	50.0	50.0	50.0	100.0	0.0	100.0	0.0	32.5	89.0
Philippines (n=1)[†]	24	7	100.0	100.0	0.0	100.0	0.0	0.0	100.0	32.0	100.0
Poland (n=1)[†]	23	8	0.0	100.0	0.0	0.0	100.0	0.0	0.0	33.0	93.3
Portugal (n=4)	22	8	25.0	25.0	75.0	25.0	75.0	75.0	0.0	33.0	97.1
Romania (n=1)[†]	23	9	0.0	0.0	100.0	100.0	0.0	0.0	100.0	30.0	82.4

Legend: [†] Countries with single-student participation. [‡] Mean ages and completed terms rounded down to the nearest whole number. ŧ Data unavailable due to survey incompletion.

Continue in next page...

Table 1 (Continued) Participating Countries' Demographics, Mean Attitude Scores, and Mean Knowledge Scores.†

Russian Federation (n=1)†	30	12	0.0	100.0	0.0	100.0	0.0	0.0	100.0	30.0	88.2
Saudi Arabia (n=1)†	24	12	0.0	100.0	0.0	100.0	0.0	100.0	0.0	21.0	85.7
Singapore (n=2)	23	3	0.0	50.0	50.0	100.0	0.0	100.0	0.0	30.5	100.0
Slovakia (n=1)†	21	4	0.0	0.0	100.0	0.0	100.0	100.0	0.0	25.0	88.2
Spain (n=1)†	32	13	0.0	100.0	0.0	0.0	100.0	100.0	0.0	34.0	93.8
Sweden (n=3)	24	4	66.7	0.0	100.0	66.7	33.3	100.0	0.0	35.0	100.0
Trinidad and Tobago (n=2)	21	4	0.0	0.0	100.0	100.0	0.0	50.0	50.0	25.0	96.4
Tunisia (n=5)	22	5	80.0	20.0	80.0	40.0	40.0	20.0	60.0	32.0	93.7
Turkey (n=1)†	20	4	100.0	100.0	0.0	0.0	100.0	100.0	0.0	33.0	93.8
United Kingdom (n=7)	22	5	42.9	28.6	71.4	42.9	57.1	85.7	0.0	32.9	91.7
United States (n=68)	27	7	42.6	54.4	45.6	39.7	52.9	0.0	97.1	29.9	93.6
All countries	23	6	41.1	42.1	57.2	44.5	49.7	49.3	42.5	31.0	92.4

Legend: † Countries with single-student participation. ‡ Mean ages and completed terms rounded down to the nearest whole number. † Data unavailable due to incomplete survey.

Table 2. Results of Two-sample T-Tests for Differences in Attitudes.*

Characteristic	Mean Attitude Score	p-value
Self-identified religiousness		
Yes (n=128)	29.2	<0.001
No (n=143)	31.6	
Legality of prostitution in country of intended practice		
Legal (n=140)	31.5	<0.001
Illegal (n=133)	29.3	
Prior education in occupational health or social determinants of health †		
Yes (n=118)	30.9	0.19
No (n=135)	30.2	
Belief that prostitution is common in country of intended practice		
Yes (n=163)	30.7	0.51
No (n=60)	30.2	
Obtained/currently pursuing a graduate degree outside of medicine ‡		
Yes (n=87)	30.2	0.35
No (n=197)	30.7	

Table 3. Results of Two-sample T-Tests for Differences in Knowledge.*

Characteristic	Mean Attitude Score	p-value
Self-identified religiousness		
Yes (n=128)	93.0	0.28
No (n=143)	91.7	
Legality of prostitution in country of intended practice		
Legal (n=140)	92.1	0.61
Illegal (n=133)	92.7	
Prior education in occupational health or social determinants of health †		
Yes (n=118)	93.7	0.09
No (n=135)	91.5	
Belief that prostitution is common in country of intended practice		
Yes (n=163)	91.8	0.50
No (n=60)	92.9	
Obtained/currently pursuing a graduate degree outside of medicine ‡		
Yes (n=88)	93.0	0.43
No (n=204)	92.1	

Legend (For Table 2 and 3): * Data for participants who selected "uncertain" or "decline to answer" were excluded from analysis. † Of all participating students, 40.4% (n=118) had previous education in social determinants of health or occupational health, 46.2% (n=135) did not, and 9.2% (n=27) were uncertain. ‡ Of all participating students, 30.1% (n=88) had completed or were pursuing a graduate degree other than medicine at the time of completing the survey. Additional degrees included Public Health (43.2% of those with additional degrees, n=38), the Biological and Life Sciences (30.7%, n=27), Business or Public Relations (5.7%, n=5), Education (5.7%, n=5), and others. Mean ages and completed terms were rounded down to the nearest whole number.

work,[7] factors to consider may also include: presence of protective rather than solely punitive laws; variability in circumstances, such as human trafficking or sexual abuse; and, of course, the media by which the legal environment is conveyed to the public to shape attitudes and opinions.[8-10] The variability in specific laws, regulation, enforcement, and influence on public attitudes means any relationship between the legal environment and medical student attitudes must be explored locally.

Despite the limitations of this study in making generalizations about medical students worldwide, an interesting outcome is the lack of association between educational background and attitudes toward female sex workers. Therefore, perhaps our focus should shift to spheres of influence outside formal education/training. Because of the vast regional differences in how socioeconomic status, religion, and legal frameworks shape knowledge and attitudes, localized studies, rather than large, global studies, may be more effective in understanding how attitudes are created and perpetuated in society. The authors want to thank the writers of the letter to the editor once again for facilitating this ongoing discussion. We also invite future collaboration to further explore how medical student attitudes toward sex workers are shaped and, therefore, how interventions can be targeted regionally to improve care and public health outcomes.

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Acknowledgments: The authors would like to thank the original letter writers for taking interest in their article and for furthering the discussion on the importance of quality, compassionate care for female sex workers.

Conflict of Interest Statement & Funding: The Author has no funding, financial relationships or conflicts of interest to disclose.

Cite as: Nakagawa JT, Akpinar-Elci M. Reply to Letter to the Editor, "Response to Medical Students' Attitudes towards Female Sex Workers". Int J Med Students. 2014 Nov-2015 Mar;3(1):74-7.