eISSN 2076-6327

IJMS

# International Journal of Medical Students

Year 2013 | Volume 1 | Issue 1

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INTERNATIONAL JOURNAL *of* MEDICAL STUDENTS

***International Journal of Medical Students***

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International Journal of Medical Students
Year 2013 - Volume 1 - Issue 1

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IJMS

# International Journal *of* Medical Students

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The Journal receives contributions and unpublished manuscripts of Original Articles, Short Communications, Reviews, Case Reports, Interviews, Experiences and Letters, which are reviewed by experts (Peer-Reviewers) who have previously published similar research. This supports the quality and validity of the results. The review time delay in most cases has been two to four months depending on the diligence of Peer-Reviewers and Authors.

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ISSN Electronic Version 2076-6327



Designed and published in Huacho, Lima, PERU.

International Journal of Medical Students

Year 2013 • Volume 1 • Issue 1

Int J Med Students 2013;1(1)

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Editorial

# The International Journal of Medical Students, a Platform for Medical Student Research Worldwide

Juliana Bonilla-Velez[1,2,3], Américo Peña-Oscuvilca[1,4], Ilyas Sahin[1,5,6], Whitney S. Cordoba-Grueso[3], Martin E. Fernandez-Zapico[7].

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It is our great honor to present to you the first issue of the International Journal of Medical Students, IJMS, a peer-reviewed open-access journal, created to share the scientific production and experiences of medical students worldwide.

Research has been historically recognized as the driving force of medical progress. As evidence-based medicine becomes progressively an integral part of clinical practice, trends in medical education demand healthcare providers to be versed in the scientific method, as well as become active contributors to the generation of knowledge. The inherent social responsibility of clinical practice implies that gaps in knowledge identified in providing care can only be judiciously addressed through medical research. As a result, there has been an increasing interest in educators and medical students to become involved in research opportunities at earlier stages of their education as a way to foster scientific initiative concurrent to clinical training. Consequently governments, academic medical associations such as the Association of American Medical Colleges, major academic institutions, and medical student associations have recognized the importance of promoting the involvement of medical students in research.

The increased scientific production of medical students has led to the development of meetings especially designed to facilitate the presentation of their work. To a lesser extent, students can often publish their findings in the medical literature, but existing medical student journals currently represent local universities, regional associations, or are housed under recognized journals as spaces to share only opinions, experiences and advice. Thus, the IJMS emerges to give a voice to those medical students who actively participate in research and contribute to the progress of medicine and the service of their communities by creating the first international scientific platform of the highest scientific quality for the publication of their work.

The IJMS has its origins in the XXIV International Scientific Congress *(XXIV Congreso Científico Internacional)* of the Latin American Federation of Medical Students' Associations (FELSOCEM) in 2009. Initial strategies were discussed among medical students involved in the Peruvian Medical Students' Scientific Society (SOCIMEP), the International Federation of Medical Students' Associations – Peru (IFMSA-Peru), the Association of Scientific Societies of Medical Students from Colombia (ASCEMCOL), the European Medical Students' Association (EMSA), and the International Federation of Medical Students' Association (IFMSA). We are proud that this project, initially started in Latin America, has now been embraced by students around the world.

Our team is led by the Executive Committee, composed of the Editor in Chief, Américo Peña-Oscuvilca (SOCIMEP), Associate Editor, Juliana Bonilla-Velez (ASCEMCOL), and Scientific Editor, Ilyas Sahin (EMSA). They form the Editorial Board in conjunction with our Mentors, renowned physician scientists from the most distinguished institutions; Senior Editors or Advisors, who are physicians starting their careers as investigators; and Junior Editors, who are medical students with experience in research and the publication process. Furthermore, the Support Committee of Public Relations and Communications includes the Director, Whitney S. Cordoba-Grueso, and Ambassadors of IJMS, who are medical students from different regions of the world who promote the journal to medical students and physicians worldwide.

Our primary goal is to be an international divulgation tool for medical students using the highest standards of scientific publication. The Journal is licensed under a Creative Commons Attribution 3.0 License and its editorial policy is based on the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* published by the International Committee of Medical Journal Editors. The IJMS receives manuscripts where there has been participation of at least

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one medical student and presents information relevant to medical education and medicine, giving priority to scientific accuracy, novelty and relevance to the medical student and medical community as a whole. We welcome submissions of Original Articles, Short Communications, Case Reports, Reviews and Letters to the Editor. We also have a special section where students may share interviews with leaders in medicine or other Experiences.

In IJMS we strive to promote student training in research and editorial processes through several strategies. For authors, our tutoring system provides feedback on how to improve their manuscript to potentially achieve publication. For junior editors, we provide an exceptional experience to develop skills on the critical evaluation of manuscripts under the guidance of expert editors, as well as on the internal functioning of a peer-reviewed journal. Finally, for Ambassadors it serves as an opportunity to participate in research-oriented initiatives and to share the culture of investigation with their peers, all within an environment of international collaboration and cultural exchange.

As proof of the importance of this initiative among medical students, several national and regional student-led organizations have become Partners of IJMS, recognizing IJMS as their official publication and providing their institutional support. Our Partners include ASCEMCOL (Colombia); the Annual International Medical Students Meeting (AIMS Meeting, Portugal); the Bio-Medical Students' Research Initiatives (BMSRI, India); the Medical-Academic Congress of Brazilian Northeast and Medical-Academic Congress of Piauí (COMAPI, Brazil); the Georgian Young Medics' Union (GYMU, Georgia); the International Student Medical Congress in Košice (ISMCK, Slovak Republic); and the Young European Scientist Meeting (YES MEETING, Portugal, Europe); and this list is continually expanding.

We are immensely proud to have assembled such a rich and experienced support system that continually helps us in our mission of truly becoming the pioneers of medical student publications, and that bring together medical students and physicians from 31 different countries around the globe. We would like to thank very specially Dr. Christian A. López-Castillo, Ahmad Adi, Dr. Jorge E. Gómez-Marín and Dr. Alfonso J. Rodríguez-Morales for their significant guidance and support in setting up this project as well as our Reviewers and Advisors for believing in this initiative and supporting it with their experience and knowledge.

We are grateful for their contributions in the formation of the future physician scientists of the world.

Without further ado, we present to you the IJMS, hoping this will become a defining moment in the history of medical student research.

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

**Cite as:**
*Bonilla-Velez J, Peña-Oscuvilca A, Sahin I, Córdoba-Grueso WS, Fernandez-Zapico ME. The International Journal of Medical Students, a Platform for Medical Student Research Worldwide. Int J Med Students 2013;1(1):6-7.*

IJMS International Journal of Medical Students

Original Articles

# Developing a Protocol for Medical Student-Organized Community-Based Hypertension Screening Programs

Vishal P. Varshney[1], Tyrone Harrison[1], Michal Szymczakowski[1], Matthew Grossi[1], Charlotte Jones[2].

## Abstract.

**Background:** Hypertension screening programs have been effective in raising awareness and identifying people who are otherwise unfamiliar with their disease. We aimed to develop a resource-minimal, evidence-based protocol for a novel medical student-organized hypertension-screening program capable of community implementation. **Methods:** Eighty-one medical students had their blood pressure measured once using an automated machine and once using the manual auscultatory method. Bland-Altman plots compared agreement between measurement techniques. **Results:** No significant difference between manual and automated techniques was noted in the measurement of systolic blood pressure, but was noted for diastolic blood pressure. **Conclusions:** In the context of a community-based screening program, automated and manual measurements may be used interchangeably to obtain an accurate measure of systolic blood pressure. A medical student-organized community-screening program is an effective way to screen large numbers of people in a short amount of time.

**Keywords:** Hypertension; Mass Screening; Blood Pressure Monitoring, Ambulatory; Students, Medical (Source: MeSH, NLM).

## Introduction.

The adverse effects of high blood pressure (hypertension) have been well established.[1-3] Hypertension, defined in Canadian guidelines as an elevated blood pressure above 140 mmHg systolic and/or 90 mmHg diastolic,[4] is estimated to cause more than one-eighth of all deaths worldwide, and is considered to be the leading risk factor for death in the world and a major risk factor for cerebrovascular, cardiac and other vascular diseases.[3,5] While the level of hypertension control in Canada has risen considerably over the last 20 years,[3] Thompson et al. revealed that at least 30% of Ontarians 18 years of age and older have uncontrolled hypertension or are unaware they have hypertension.[2] Hypertension screening programs have been shown to be an effective way of raising awareness, identifying and managing patients who may otherwise not know of their disease.[6,7]

Hypertension screening programs utilizing existing community resources to conduct door-to-door and mobile screening assessments have been in use since the 1970's.[8,9] More recently, community-based blood pressure programs, held in local pharmacies and specifically recruiting senior citizens, have shown that using a team-based approach with nurses, pharmacists and trained volunteers can effectively raise awareness, identify and manage seniors with hypertension.[7] Although not the focus of our study, these can be seen as a way to minimize white-coat hypertension, defined as a continuous elevation in blood pressure measurements in a clinical setting, which is estimated to have a prevalence of up to 25%.[10] Building on these successes, while also minimizing the resource-intense nature of these and other screening programs, our project aimed to develop an evidence-based protocol and technique for a novel medical student-organized hypertension screening program capable of being implemented in any public location.

Medical student-run public health initiatives have shown success in contributing to both medical education and patient care.[11] In our study, we used two methods to obtain blood pressures: manual auscultatory measurement (using calibrated aneroid machines and stethoscopes) and automated measurement (using a validated oscillometric blood pressure device), in order to determine if there were significant differences in blood pressure measurements between these techniques and to evaluate their ease of use in a community setting. The implications of our project are profound in that medical students are taught to take blood pressures early on in their training, and can conduct community-based blood pressure screening programs without needing significant economic resources. Adhering to a standard, evidence-based protocol means that any medi-

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*Submission: 2012, May 3.*
*Accepted: 2012, October 14.*
*Process: Peer-Reviewed.*

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cal school with basic equipment could coordinate screening programs in their communities, and be successful in reaching out to members of the community that may not have been identified as hypertensive otherwise.

## Methods.

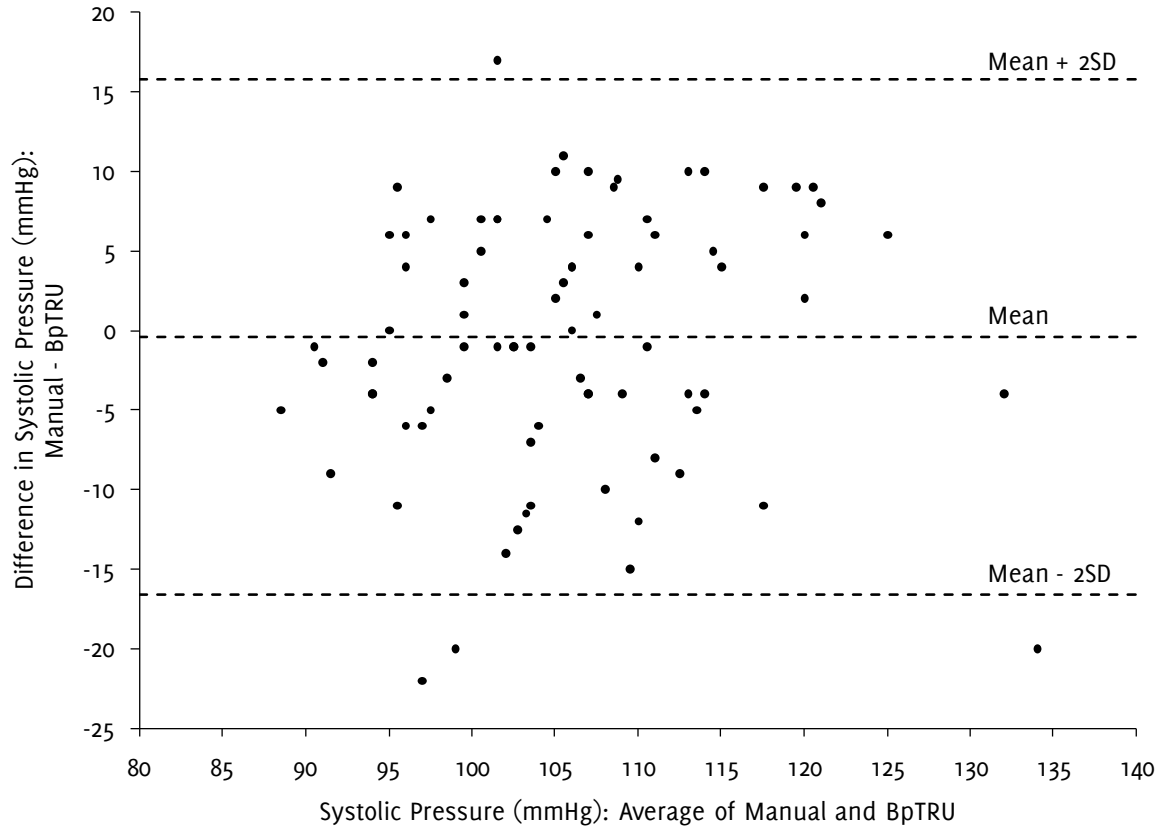
The protocol was approved by the Conjoint Health Research Ethics Board at the University of Calgary. Eight first year medical students met with their supervisor (CJ), reviewed CHEP guidelines and together designed and implemented the screening program. 81 2nd year medical students volunteered for the study through email. Consenting participants were excluded if they smoked, had caffeine or engaged in physical exercise one half-hour prior to measurement. Participants had their blood pressure measured twice, once with the automated technique ("Automated") using the BpTRU device (BpTRU Medical Devices, Coquitlam BC, Canada) and once with the manual auscultatory technique ("Manual") using calibrated aneroid machines (WelchAllyn Trimline Medical Products, Branchburg NJ, USA) and taken by medical students. The order in which their blood pressures were measured was randomly determined (www.random.org). Manual measurements were taken as per the Canadian Hypertension Education Program (CHEP) guidelines (4), and participants were required to rest a minimum of 5 minutes, before and between measurements with both devices. Three manual measurements were taken, with the last two measurements averaged for analysis. Six automated measurements were taken, with the last five measurements averaged for analysis.

Manual and automated measurements were compared and analyzed using Bland-Altman plots. In biostatistics, Bland-Altman plots have been shown to analyze agreement between two different measurement types in a single person (12). As neither manual nor automated measurement techniques will give the "true" value of blood pressure, these plots help in determining whether the measurements are comparable. In the context of establishing a community-based screening program, we sought to observe the agreement between automated measurements, which are quicker and easier to obtain, and manual measurements, which are commonly done in clinics. A post-event focus group was held with volunteers to determine how the process could be improved.

## Results.

Eighty-one medical students consented to participate. Figure 1 shows all but four data points within the 95% limits of agreement. The mean difference (manual – BpTRU in mmHg) in systolic blood pressure (SBP) between devices was -0.42 mmHg (95% confidence intervals: -2.19 to 1.34).

***Figure 1.*** *Bland-Altman Plot for Systolic Blood Pressure (n=81). Mean difference = -0.42 mmHg (95% CI: -2.19 to 1.34).*



There was no observable trend toward higher or lower readings regardless of the device used, average SBP or order of the blood pressure assessment. Variability was consistent across the range of SBP (85-135 mmHg).

Figure 2 shows that all but two data points are within the 95% limits of agreement. The mean difference is significant (and clinically relevant), at -4.92 mmHg (95% CI: -6.45 to -3.29). There was a tendency for the difference between methods to increase as diastolic blood pressure (DBP) increased. The variability around the mean difference remained constant across the range of DBP (55-85 mmHg).

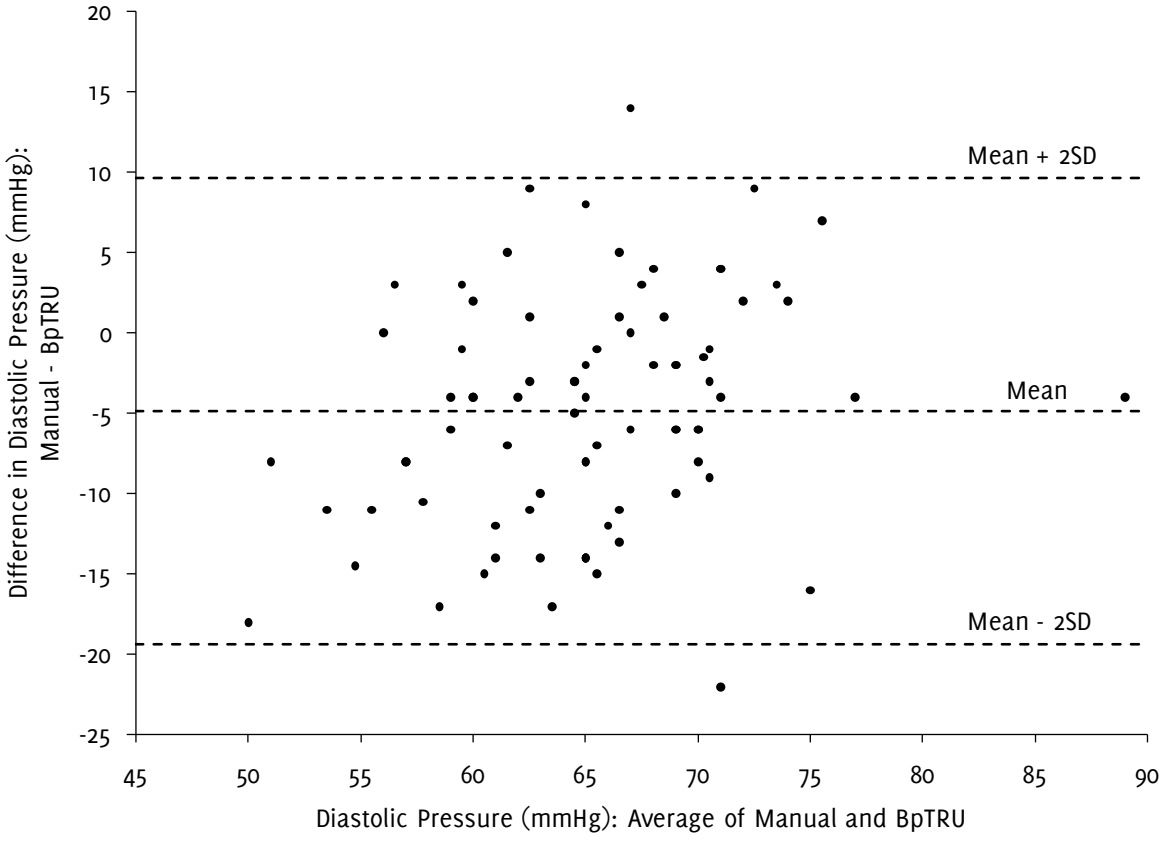
## Discussion.

Bland and Altman demonstrated that, in the context of comparing blood pressure measurements, there could still be poor agreement between variables despite relatively high correlation coefficients. Correlation coefficients measure association and not agreement.[12] This explains our reasoning for not presenting our data with regression analysis. Bland-Altman plots are constructed with the average of values from the two measurements on the x-axis and the difference in values between the two measurements on the y-axis. Given that different hypertension guidelines highlight different management options for control of systolic and diastolic pressures, data was presented separately for diastolic and systolic pressures to observe the agreement between automated measurements, which are quicker to obtain, and manual measurements, which are commonly done in clinics - a main goal of our intended community-based screening program.

The results indicate that there is no significant difference between manual and automated measurements in determining systolic pressure, but diastolic blood pressure measurements shows a larger, and significant, mean difference. The 95% confidence intervals also validate this. Increases in SBP have shown to be linearly related to cardiovascular mortality at all ages, and SBP has been recommended to become the major criterion for diagnosis, staging, and therapeutic management of hypertension.[13,14] This suggests that in the context of a community-based screening program, manual or automated measurements can be used interchangeably and comparably for a subject to determine their systolic blood pressure, and thus, gain insight into their overall cardiovascular health.

Possible reasons as to why diastolic blood pressure measurements had a larger mean difference may be because Korotkoff sounds for diastolic pressure are difficult to auscultate in a community-based setting.[15] In the manual auscultatory technique, five unique phases of sounds have been

***Figure 2.*** *Bland-Altman Plot for Diastolic Blood Pressure (n=81). Mean difference = -4.92 mmHg (95% CI: -6.45 to -3.29).*



described: Phase I represents the first appearance of faint, repetitive, clear tapping sound which gradually increase in intensity for at least two consecutive beats (the systolic pressure); Phase II is a brief period where the sounds soften and "swish"; Phase III is the return of sharper sounds (clinical significance yet to be determined); Phase IV is the distinct abrupt muffling of sounds, which become soft and blowing in quality; and Phase V is the point at which all sounds finally disappear (the diastolic pressure).[15] The "diastolic dilemma" is a well-described phenomenon that expresses uncertainty about the diastolic endpoint, in that Phase IV sounds may coincide with, or occur at pressures as much as 10mmHg higher than Phase V sounds.[15,16] Given the subjective component in distinguishing between Phase IV and Phase V sounds, especially in an environment with much ambient noise, manual diastolic pressures did show less agreement with automated diastolic pressures.

The possibility exists for a community-based hypertension-screening program to possibly reduce the prevalence of white-coat hypertension, although further research is needed. Currently, ambulatory blood pressure monitoring is diagnostic for patients with elevated clinic blood pressures.[17] If screening blood pressure in the community can remove the suggested conditioned response that results from endogenous pressor release incited in the clinical setting,[3,10] there could be a significant decrease in the number of false positive hypertension diagnoses that are solely based on clinic measurements. More research is suggested in this area.

We successfully accommodated 81 participants within a 2-hour span, with only 8 volunteers. Operational costs for our specific set-up were extremely minimal, with the only costs being those of the BpTRU machines. An area with much ambient noise and high traffic was specifically sought for our study so as to best simulate a community environment. The entire set-up and take-down process required minimal effort from volunteers, and was estimated to be easily reproducible in other settings, such as shopping malls, schools, community centers and office tower lobbies. The post-event focus group identified front-desk organization and further training with the automated machines as areas of improvement for future projects. The ease with which one can establish a medical student-organized hypertension screening program in the community was reassuring, and we look forward to further research comparing community-based blood pressure assessment with that of the standard office setting to further validate the protocol. Student-led programs such as this may prove to be of benefit the community and public health.

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**Acknowledgements**

*To Leanne Ross, Research Coordinator and Statistician; help with statistical analysis and project coordination. To Reena Hansen, Kimchi Nguyen, Shawna Jensen, Nicholas Field, Laura Coughlan and Elizabeth Kelly, Third year medical students.*

**Funding**

*Calgary Medical Students Association (CMSA) Endowment Fund.*

**Conflict of Interest Statement**

*The Authors have no conflict of interest to disclose.*

**Cite as:**

*Varshney VP, Harrison T, Szymczakowski M, Grossi M, Charlotte J. Developing a Protocol for Medical Student-Organized Community-Based Hypertension Screening Programs. Int J Med Students 2013;1(1):8-11.*

IJMS International Journal of Medical Students

Original Articles

# Hormone Replacement Therapy and Dry Eye in Post Menopausal Women: Study in a Tertiary Centre in Malaysia

Norshamsiah M. Din[1], Siti H. B. Sa'aid[2], Lam C. Shen[2], Yap S. Shu[2], Marina B. A. Rahman[2], Aini B. M. Azmi[2], Chang S. Thing[2], Mushawiahti Mustapha[1], Ropilah A. Rahman[1].

## Abstract.

**Background:** Menopause involves decrease in the body estrogen level. There are many disorders associated with estrogen deficiency state. Postmenopausal women frequently report dry eye symptoms due to the decrease in the level of circulating estrogen hormone. Hormone replacement therapy (HRT) is given to alleviate some of the menopausal effects. This study aimed to compare the tear production between postmenopausal women treated with or without HRT. **Methods:** This cross-sectional study was performed on 140 participants attending various clinics in Universiti Kebangsaan Malaysia Medical Centre (UKMMC) namely the obstetric and gynecology, Surgery, Orthopedic and Otorhinolaryngology clinics over a period of 3 months. The subjects were either with or without HRT. Schirmer's Test strip was used to measure the tear quantity. Dry eye was defined when the length of the moistened area on the strip is less than 5 mm. **Results:** The results showed significant difference in tear quantity in postmenopausal women treated with or without HRT (p=0.003). No correlation was observed between tear quantity and duration of HRT consumption, (p=0.217).No significant correlation was also found between the tear quantity and duration of menopause (p=0.150). **Conclusions:** Our results suggested that HRT helps in improving tear production in postmenopausal women regardless of the duration of HRT consumption or menopause However, duration of HRT consumption or menopause exert no significant effect on the tear quantity.

**Keywords:** Postmenopausal; Women; Hormone Replacement Therapy; Dry Eye Syndrome (Source: MeSH, NLM).

## Introduction.

Dry eye syndrome is one of the most common clinical entities encountered by eye care professionals, especially among middle-aged and older adults. Dry eye syndrome, also known as keratoconjunctivitissicca, or more recently dysfunctional tear syndrome, has been defined in various ways as the understanding of the disease process evolved. Dry eye syndrome is due to disturbances of the lacrimal functional unit, which comprises of lacrimal glands, ocular surface (cornea and conjunctiva), eyelids, meibomian glands, and associated sensory and motor nervescausing alterations in the volume, composition, distribution or clearance of the tear film.[1]

Menopause is defined as a phase during which there is complete menstrual cessation for at least one year with elevated Follicular Stimulating Hormone (FSH) serum levels (>40 IU/L).[2] The hormonal changes may lead to decreased tear production which is the root of dry eye syndrome. About 60% of menopausal women are affected by dry eyes.[3] The symptoms of dry eye, namely dryness, itchiness, photophobia, blurring of vision, foreign body sensation and tearing may cause considerable discomfort to patients and subsequently interfere with their quality of lifeUntreated dry eye syndrome increase the susceptibility of the eyes towards infection as well as causing serious visual impairment.[1] HRT has been well accepted to improve the quality of life among the postmenopausal women.[4]

Dry eye syndrome is diagnosed by multiple methods such as non-invasive tear break up time, Schirmer's test and fluorescein clearance test.[5] Schirmer's Test (©Haag-Streit UK) remains the most popular and practical method in many clinical settings as it was also reported to correlate well with the basal tear turnover and tear flow.[6] It is also convenient and cost-effective. At a cut off value of 5 mm, the sensitivity and specificity were reported to be 80% and 53%, respectively.[7]

*Submission: 2011, Nov 27.*
*Accepted: 2012, May 5.*
*Process: Peer-Reviewed.*

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This study aimed to determine the association between HRT and tear production in postmenopausal women and to observe whether duration of menopause and HRT usage had any effect on the tear quantity.

## Methods.

This cross-sectional study was performed on postmenopausal women, in the department of Obstetrics and Gynecology (O&G), Surgery, Orthopedic and Otorhinolaryngology clinics in UKMMC (Universiti Kebangsaan Malaysia Medical Centre). The subjects comprised of 3 major ethnic races in Malaysia i.e. Malay, Chinese and Indian. These subjects were either with or without HRT. The sample size was calculated from Sample Size Calculations in Clinical Research. A total of 140 patients who were with or without HRT were assessed over a period of 3 months. Prior ethical approval was obtained from the ethics and research committee of the Faculty of Medicine, Universiti Kebangsaan Malaysia (FF-017-2009).

The inclusion criteria were postmenopausal women diagnosed within the last 10 years, with or withoutHRT. Patients with systemic disorders known to cause dry eyes such as Rheumatoid Arthritis, Diabetes Mellitus, Thyroid Disease, AIDS, Graft Versus Host Disease, Parkinson's Disease, patients who had underwent bone marrow transplant, patients on medications known to cause dry eyes like anticholinergic medications, Non-steroidal Anti Inflammatory Drugs, Beta-blocker and radiation therapy, patients with known ocular surface diseases like Herpes Simplex Keratitis and Herpes Zoster Ophthalmicus, topical eye drop users and patients who had recent ocular surgery within 3 months and contact lens wearer were excluded.

Following a written informed consent, a brief ocular and medical history was obtained followed by a brief external eye examination. Schirmer's Test was then performed by trained medical students. Following 5 minutes of topical anesthesia application with Proparacaine Hydrochloride 0.5%, A Schirmer's strip was placed at the inferior conjunctival fornix by placing the bent round wick end of the test strip at the temporal one–third of the lower eyelid margin to avoid corneal touch. The strip was left for 5 minutes while permitting normal blinking or eye closure. The length of the moistened area of the strip was then measured using a millimeter scale. A reading of less than 5 mm was considered to be dry.

A total of 140 patients with 70 patients in each arm of patients with and without HRT were recruited to make the power of study to be 95%. Data was analyzed using the Statistical Package for Social Science (SPSS) standard version 13.0. T test, chi square and Pearson correlation test was used for data analysis. A value of $p<0.05$ was considered significant.

## Results.

A total of 140 patients were recruited. There was equal number of participants in both groups of patients with or without HRT. Age ranged from 46 to 74 years old. The mean age was 57.89±11.89 years old. The Malays (57.9%) formed slightly more than half of the study population followed by Chinese (34.3%), Indian (6.4%) and others (1.4%, Table 1).

Among the HRT users, almost three quarter (74.3%) of the patients do not have dry eyes as compared to the non HRT users in which 50% were found to have dry eyes. This difference was found to be statistically significant ($p = 0.003$) (Table 1, Figure 1).

Among those without HRT, there was no significant association between the occurrence of dry eyes and the duration of menopause. ($r=-0.174$, $p=0.15$). For those on HRT treatment, Pearson correlation test also showed no significant association between the tear quantity and duration of HRT consumption (r value = -0.133 and $p=0.271$, Figure 2 and 3).

## Discussion.

The role of HRT inhelping tear production is not well understood. Many clinical studies agreed that administration of

***Table 1.*** *Demographic Data.*

| | Dry eye | Non Dry eye | Total | *p* value |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Mean (SD) | | | 57.89 ± 11.89 | |
| **Race, n (%)** | | | | 0.870 |
| Malay | | | 81 (57.9) | |
| Chinese | | | 48 (34.3) | |
| Indian | | | 9 (6.4) | |
| Others | | | 2 (1.4) | |
| **HRT, n (%)** | | | | 0.003 |
| HRT Users | 18 (25.7) | 52 (74.3) | 70 (50) | |
| Non HRT users | 35 (50.0) | 35 (50.0) | 70 (50) | |

estrogen increases both the quantity and quality of tears.[8,9] Improvement in tear break-up time (TBUT) and Schirmer's test was also reported after the constitution of hormonal therapy.[10] Lacrimal secretion increases with the usage of combination of estrogen and progesterone treatment.[11] We includedpatients on all types of HRT whether estrogen alone or combined with progesterone.

Despite many supporting clinical researches on the benefit of HRT on dry eyes symptoms, there was also contradicting data suggesting estrogen as an exacerbating factor for dry eyes.[12,13] The contradictory results may be attributed to the different tools used to define dry eyes.

Dry eye syndrome is common in the older population.[14] But it remains difficult to diagnose because of the lack of a gold standard diagnostic testand it is complex etiology and pathophysiology.[15] Measurement of tear osmolarity might provide a "gold standard" of diagnosis, but a practical tear osmolarity test is not available, to date.[16]

As in the present study, Schirmer's strip is still the most clinically reliable method in managing dry eyes cases.[5,6] The Schirmer test is widely used clinically for assessing tear production.[17,18]

Although there are many small studies which fail toprove the beneficial effect of HRT for dry eyes, the association of menopause and increasing symptoms of dry eyes has been well elaborated.[13,19] We found higher incidence of dry eyes in menopausal women without HRT treatment as compared to those on hormonal therapy. Even though the duration of treatment was not found to be an important factor in our clinical setting, having HRT on board does help to eliminate dry eyes among post menopausal women in our population.

Argument exists on the fact that the duration of menopause increases dry eyes syndrome.[20] This does not seem to be true in our population as the duration of menopausedoes not increase the incidence of dry eyes among non HRT user. The findings in the present study support the ocular importance of HRT in elderly women.

Apart from continuous prescription of ophthalmic lubrication, reassurance and discussion on the disease may help to alleviate anxiety and offer additional information for our patients. This cross sectional study however may not be able to elaborate further on the correlation of symptoms and severity of the disease.

Further analytic study in the same setting would be able to evaluate thoroughly the significance of dry eyes in this group of patient. Apart from hormonal factor, consideration of other confounding factors such as surrounding environment and individual social activity would certainly give more useful information as to the effect of prolong HRT consumption or duration of menopause on dry eyes.

In conclusion, HRT use is associated with improved tear production in postmenopausal women. However, the duration of HRT consumption is not associated with improved dry eye condition. Schirmer's test is still a useful clinical method to supplement other diagnostic criteria such as tear break-up time (TBUT) and symptoms-based questionnaire, to further confirm the diagnosis of dry eye.

***Figure 1.*** *Comparison of the occurrence of dry eyes between HRT users and non HRT users. There was significant difference between these two groups. HRT users showed significant reduction in the number of patients with dry eyes. (p=0.003)*

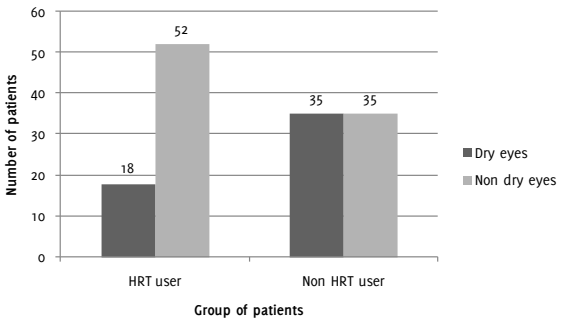



***Figure 2.*** *Relationship between duration of menopause in non HRT users with dry eyes. There was no significant association between the occurrence of dry eyes and the duration of menopause. (Pearson correlation test; r=0.174, p=0.15).*

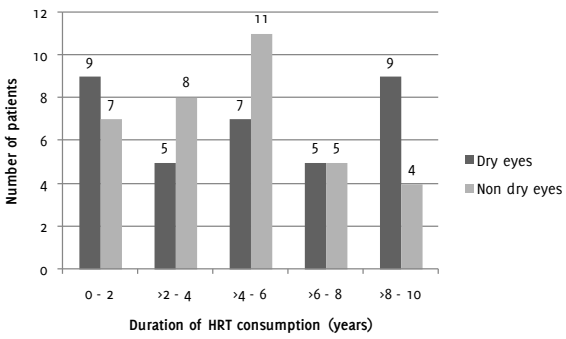
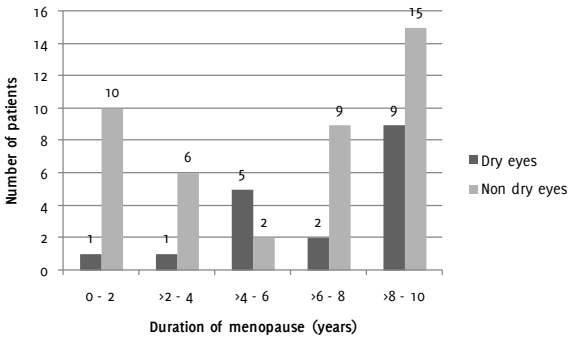



***Figure 2.*** *Relationship between duration of HRT consumption and dry eyes. There was no significant association between the occurrence of dry eyes and duration of HRT consumption. (r value = -0.133 and p=0.271).*



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**Acknowledgements**

*We would like to thank Prof. Zainul Rashid bin Mohamad Razi and Ass. Prof. Dr. NorAzlin Ismail from the Department of Obstetric and Gynecology, Ass. Prof. Dr. Razman Jarmin from the Department of Surgery, Prof. Dr. Sharaf Ibrahim from the Department of Orthopaedics, Associate Prof. Dr.Asmabt Abdullah from the Department of Otorhinolaryngology, UKMMC and all the staffs for their cooperation and support.*

**Funding**

*A grant was received from the Faculty of Medicine fund, Universiti Kebangsaan Malaysia. (FF-017-2009).*

**Conflict of Interest Statement**

*The Authors have no conflict of interest to disclose.*

**Cite as:**

*Din NM, Sa'aid SHB, Shen LC, Shu YS, Rahman MBA, Aznin ABM, et al. Hormone Replacement Therapy and Dry Eye in Post Menopausal Women: Study in a Tertiary Centre in Malaysia. Int J Med Students 2013;1(1):12-5.*

IJMS International Journal of Medical Students

Original Articles

# Effect of an Educational Booklet on Knowledge and Attitude Regarding Major Depressive Disorder in Medical Students in Delhi

Medha Goyal[1], Charu Kohli[1], Jugal Kishore[1], Ram C. Jiloha[1].

## Abstract.

**Background:** Depression is one of the most common mental disorders affecting people in the world. It is also a growing concern in younger population particularly medical students. There are many pharmaceutical interventions for treatment of depression but there is paucity of data to determine the effect of educational intervention on the knowledge, attitude and help seeking behaviour regarding depression among medical students. **Methods:** An interventional study was carried out among randomly selected 100 medical students except interns over a period of 6 months from March-August 2011 in a medical college in Delhi to assess the effect of educational booklet on knowledge and attitude about depression. Data was collected using pre-tested questionnaire and analyzed using SPSS version 16 software. Statistical significance in pre and post intervention proportions was determined using Mc Nemar test (MN) and for other proportions Chi-square test. **Results:** The study shown that only 71% of subjects knew that depression is a disease in pre intervention phase, which rose to 88% in post intervention phase (p=0.01). Knowledge of symptoms and treatment significantly improved such as trouble falling asleep or too much sleep (p=0.03), feeling tired or decreased energy (MN=17.6, p=0.01), feeling bad about self (MN=21.8, p=0.01), speaking slowly other can notice (MN=19.1, p=0.01) and can be treated by improving awareness (MN=8.6, p=0.03), and anti-depressants do not cause much of side effects (MN=17.3, p=0.01). Most common reasons for not seeking help were thinking that there is lack of understanding by other people about the depression (63%), lack of confidentiality (49%), social stigma (30%), fear of rejection (26%) and time constraints (6%). Majority of students accepted the booklet for their understanding about depression where 63% considered that it improved their knowledge to great extent. **Conclusions:** Educational interventional booklet should be promoted at bigger level to help students to identify and understand the depression which may improve health seeking behavior and could decrease their suffering if they fall sick.

**Keywords:** Depressive Disorder; Pamphlets; Health Knowledge, Attitudes, Practice; Students, Medical (Source: MeSH, NLM).

## Introduction.

Depression is one of the most common mental disorders affecting 121 million people in the world. It presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy and poor concentration.[1,2] Presently, depression is already the 2nd cause of DALYs in the age category 15-44 years for both sexes combined. By the year 2020, depression is projected to reach 2nd place of the ranking of DALYs (Disability Adjusted Life Years) loss calculated for all ages, both sexes.[1] The lifetime prevalence of depression is 12.1%.[3] It accounts for 5% of total burden of disease from all causes in the world.[4] The prevalence of depression is variable in different age groups and occupation. In South Asia, 14,582 thousand DALY's loss due to depression which is 3.6% of all causes.[5] A large population-based study from South India reported overall prevalence of depression to be 15.1% after adjusting for age using the 2001 census data.[6]

Medical students are highly prone to stress, anxiety and depression as they confront significant academic, psychological and existential stressors throughout their training.[7-10] Studies have shown that level of depression is very high in medical students as compared to the general population.[11] Depression is associated with suicides and it was found that 53.6% of the medical students have suicidal ideation and 4.9% have contemplated suicide.[12]

In an intervention study in the University of Hawaii among medical students, 59.1% of them had reported depressive symptoms and 30.2% reported suicidal ideation.[13] An In-

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*Submission: 2012, May 15.*
*Accepted: 2012, July 19.*
*Process: Peer-Reviewed.*

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dian study showed overall level of depression in medical students to be as high as 39.44%.[14] A big hurdle encountered while dealing with depression in medical students is that very few of them seek help although depression is reliably diagnosed and many treatment options are available.[15] However, there are very few studies conducted among Indian medical students to assess the impact of an educational intervention on the knowledge, attitude and help seeking behaviour regarding depression.

Therefore this study was planned with an objective to assess the impact of Information Educational Communication (IEC) material in the form of a booklet on knowledge, attitude and approach to deal with depression among medical students in Delhi.

## Methods.

***Study design, participants and sampling technique***

A college based intervention study was conducted over a period of 6 months from March-August 2011 in a medical college of Delhi. Sample size was calculated on the basis of a study that the baseline knowledge about depression in medical students to be 50%.[16] It was expected to moderately increase up to 70% after intervention in the form of an educational booklet. Taking power of the study to be 80% and $\alpha$ error 5%, sample size was calculated using EPI-INFO software version 3.3.2. It came out to be 103. However, 105 medical students from different batches were selected by stratified sampling from their roll numbers. Out of 105 students enrolled, 5 students did not reported back with completed questionnaire after 1 week in spite of three reminders. Therefore only 100 students were included in the final analysis.

***Methodology***

The study was divided into three phases; pre intervention phase, intervention phase and post intervention phase. In pre intervention phase, selected students were given a self administered questionnaire. In intervention phase, students were given intervention material in form of an IEC booklet. In post intervention phase, the same students were contacted a week after giving IEC booklet. The students were again asked to fill the questionnaire. Comparison was made on the basis of response to questionnaire before and after the intervention.

***Inclusion and exclusion criteria***

All undergraduate medical students enrolled with medical college were included. The students doing internship were excluded. None of the student was seriously ill due to physical component of health or admitted in hospital.

***Study tool***

For assessing knowledge and attitude, a semi-structure questionnaire consisting of items on age, current semester of study, family type, parent's occupation, history of previous schooling and interest in pursuing medical course along with student's knowledge, attitude and perception about causes, symptoms, treatment of depression and their help seeking behavior in case they suffered from depression was prepared. The majority of items of questionnaire were based on validated instrument,[17,18] however it was tested for its feasibility and appropriateness among medical students aged 18-25 years of another medical college in Delhi.

For intervention, an IEC booklet containing information regarding various aspects of depression like symptoms, causes, risk factors, different forms, treatment options, common myths and easy techniques that could be tried prior to taking professional help, in case the student suffered from depression was developed. The content of IEC booklet was based on the standard textbook of psychiatry[19] and was approved by professional psychiatrist and public health expert. It was pretested among students of same age group who were not a part of study sample. Their suggestions were incorporated in the booklet before use in the actual study. The booklet was printed in simple language and made colorful and attractive with all major issues related to depression were dealt with.

***Statistical analysis***

The data collected was entered in MS-Excel and analyzed using SPSS software. Results were presented in simple proportions and difference between groups was assessed for their significance using statistical tests. For comparison of pre and post intervention difference, Mc Nemar test was applied while aspects, which were evaluated only once but compared with other group, their significance was assessed using chi-square test. The results were accepted as significant if "p" value was less than 0.05.

***Ethical issues***

The students were explained the purpose of the study. Information collected and identity was kept confidential and their informed consent was taken before taking information. The study was approved by the institutional ethical committee.

## Results.

Out of 100 medical students who participated in the study, with a mean age of 20 ± 1.28 years old and 48 were males. Sixty-four percent were hostellers and 36% were day scholars; 81% stated that they are pursuing medical career with self interest while 8% said parent's interest is the reason behind opting this profession.

***Knowledge about causes and risk factors***

It was found in the study that 71% of students knew that depression is a disease in pre intervention phase however, this figure rose to 88% in post intervention phase. This increase was found to be statistically significant (p=0.01). The

students who considered that old people and women are less prone to suffer from depression fell from 11% to 9% and 8% to 2% respectively after intervention.

Children do not suffer from depression was initially considered by 16% students and after intervention by 12% students. The percentage of students who felt that lower socio-economic status increases the risk of developing depression increased after the study from initial 50% to 67% , which was not significant, but the students who considered that people in contact with depressed people tend to develop odd or strange behavior decreased significantly after the intervention from 43% to 21% (p=0.01). 57% of students thought that higher education or high Intelligent Quotient (IQ) increases the risk of developing depression in post intervention phase as compared to 41% in pre intervention phase which is statistically significant (p=0.03). 97% of the subjects knew that depression is a result of dynamic imbalance of brain neurotransmitter after intervention as compared to 84% before intervention (p=0.04).

Similarly, there was a significant increase in the number of students who thought that depression results from abnormal family structure from 81% to 92% after intervention (p=0.03). Depression could be due to social circumstances was considered prior to intervention by 97% students which improved to 99% after intervention. There was an increase in percentage of students who considered poor nutritive diet, polluted air, loss of semen/vaginal secretion and god punishing for sins or wrong doing as cause of depression from initial 43%, 25%, 27% and 16% respectively to 74%, 59%, 63% and 38% respectively after intervention. Achievement oriented society was taken as cause of depression before intervention by 82% and after intervention by 91% of students (p=0.10). The fact that depression runs in family was known initially to only 44% students while after intervention, it was known to 75% (Table 1).

***Knowledge about symptoms of depression***

In regard to symptoms of depression, it was observed that 95% students knew that decreased pleasure or interest in doing things was a symptom in post intervention phase vis-a vis 86% in pre intervention phase (p=0.49). Similarly, feeling down or hopelessness was mentioned as a symptom of depression by 94% students, which after intervention increased to 99% (p=0.12). After the intervention, trouble falling sleep or sleeping too much was considered as symptom of depression by 96% as against earlier by 86% (p=0.03).There was an increase from 69% to 96% in the number of students who considered feeling tired or having decreased energy as symptom of depression after intervention (p=0.01).

Poor appetite or overeating was thought as a symptom before intervention by 79% and after intervention by 98% respondents (p=0.01). Initially 92% students responded to "feeling bad about yourself or that you are a failure or has let yourself or your family down?" as a symptom of depression, which post intervention reached 100% (p=0.01). Prior to intervention, 76% students believed that trouble concentrating on activities, such as reading newspaper or watching television was a symptom of depression, which after intervention was known to 95% students (p=0.01).

A significant increase was detected in the number of students from 59% to 89% who considered "moving or speaking so slowly that other people have noticed or being fidgety or restless" as a symptom (p=0.01). After the intervention, 98% pointed out the thoughts of being dead or hurting themselves in some way as a symptom against initial 84% (p=0.01) as shown in the Table 2.

***Knowledge about treatment of depression***

Regarding treatment of depression, there was a slight decrease in the number of students who considered depression as untreatable, from 4% to 3% after intervention. Similarly, the percentage of students who considered that depression was as well treated by spiritual and faith healers as the psychiatrists decreased from 43% to 35% in post intervention but the decrease is not statistically significant (p=0.29). The percentage of students who believed that depression can be treated by improving the awareness of patient towards his emotional feelings improved significantly from 78% to 94% (p=0.03). Comparing the response on question whether taking anti-depressants has side effects showed improvement when 92% students thought that taking anti-depressants has side effects, which declined to 66% after intervention (p=0.01). Similarly, there was but not significant decrease in the percentage of students who thought that anti-depressants are addictive from 51% to 45% in post intervention phase (p=0.48). (Table 3)

***Attitude towards depression***

Initially, 79% subjects believed that they would employ a person who had recovered from depression and after the intervention it increased to 89 % (p=0.07).The percentage of students who would be against a close relative marrying a person who has recovered from depression after the study increased from 17% to 24 % (p=0.20) but the difference is not significant statistically. The students who found themselves comfortable talking with depressed person significantly improved after the intervention from 58% to 73% (p= 0.04). The results of attitude toward depression are depicted in Table 4.

***Help seeking behavior***

Items on help seeking behavior were asked before distribution of booklet only. It was because of not to identify medical students with depression for social and ethical concerns. However, they were advised to report to psychiatry OPD if they had symptoms suggestive of depression.

*Table 1. Comparison of pre and post intervention phases on knowledge about causes and risk factors of depression.*

| Items | Pre - Intervention (%) | Post - Intervention (%) | Mc Nemar test | p Value |
|---|---|---|---|---|
| Depression is a disease | 71 | 88 | - | 0.01 |
| Older people are less prone to depression | 11 | 9 | - | 0.80 |
| Children don't suffer from depression | 16 | 12 | - | 0.50 |
| Women are less prone to depression | 8 | 2 | - | 0.10 |
| People in contact with depressed people develop strange behavior | 43 | 21 | 11.02 | 0.01 |
| Lower socio-economic class is more prone to depression | 50 | 67 | 5.68 | 0.17 |
| High IQ is a risk factor for developing depression | 41 | 57 | 4.32 | 0.03 |
| Depression is caused by | | | | |
| Imbalance of brain neurotransmitter | 84 | 97 | - | 0.04 |
| Abnormal family structure | 81 | 92 | - | 0.03 |
| Social circumstances | 97 | 99 | - | 0.62 |
| Poor nutritive diet | 43 | 74 | 17.64 | 0.01 |
| Polluted air | 25 | 59 | 20.94 | 0.01 |
| Loss of semen/vaginal fluid | 27 | 63 | 21.8 | - |
| God punishing for wrong doing/sins | 16 | 38 | 9.5 | 0.02 |
| Achievement oriented society | 82 | 91 | - | 0.10 |
| Depression runs in family | 44 | 75 | 15.78 | - |

*Table 2. Comparison of pre and post intervention phases on knowledge about symptoms of depression.*

| Items | Pre - Intervention (%) | Post - Intervention (%) | Mc Nemar test | p Value |
|---|---|---|---|---|
| Decreased pleasure or interest in doing things? | 86 | 95 | - | 0.49 |
| Feeling down or hopeless? | 94 | 99 | - | 0.12 |
| Trouble falling/staying asleep, sleeping too much? | 86 | 96 | - | 0.03 |
| Feeling tired or having little energy? | 69 | 96 | 17.64 | 0.01 |
| Poor appetite or overeating? | 79 | 98 | - | 0.01 |
| Feeling bad about yourself or that you are a failure or has let yourself or your family down? | 92 | 100 | 21.87 | 0.01 |
| Trouble concentrating on things, such as reading newspaper or watching television? | 76 | 95 | - | 0.01 |
| Moving or speaking so slowly that other people have notice being so fidgety or restless that you have been moving around a lot more than usual? | 59 | 89 | 19.1 | 0.01 |
| Thoughts that you would be better off dead or of hurting yourself in some way? | 84 | 98 | - | 0.01 |

*Table 3. Knowledge about treatment of depression in pre and post intervention phases.*

| Items | Pre - Intervention (%) | Post - Intervention (%) | Mc Nemar test | p Value |
|---|---|---|---|---|
| Depression is untreatable | 4 | 3 | - | 1.00 |
| Depression can be treated by spiritual and faith healers | 43 | 35 | 1.11 | 0.29 |
| Improved by leaving patient alone | 8 | 12 | - | 0.50 |
| Improved by change in environment | 93 | 94 | - | 1.00 |
| Improved by increasing awareness of patient towards his/her feelings | 78 | 94 | 8.6 | 0.03 |
| Anti depressants have side effects | 92 | 66 | 17.3 | 0.01 |
| Anti depressants are addictive | 51 | 45 | 0.5 | 0.48 |

Therefore items on health seeking were not assessed in post intervention phase. On asking whom they would prefer to consult if they suffer from depression, 73% students stated that they would like to seek help from a health professional like a counselor or a psychotherapist. 72% said they would like to discuss with their family members, 35% would prefer in taking help from teachers and mentors. 26% students thought that self treatment would be best for them while 20% would like to seek information from internet.

Another significant observation was reasons for not seeking help in depression. 19% of the students felt that if they go to anybody for help, be it their family members, health professionals or teachers, it would not yield any result. Another 9% felt ashamed while asking for help and a same percentage felt that time constraint is responsible for not seeking help. When asked about the problems faced while seeking help, 63% believed that the lack of understanding by other people prevent them from taking help. As many as 49% students said that greatest fear while seeking help was the lack of confidentiality. Other reasons were stigma (30%), fear of rejection (26%) and waste of their time (6%) as shown in Figure 1.

The various mediums preferred by students for seeking help were determined and it was noticed that 80% preferred face-to-face interview followed by telephone (22%), internet (17%) and letter writing (14%).

***Figure 1.*** *Greatest fear reported by study subjects for not seeking help.*

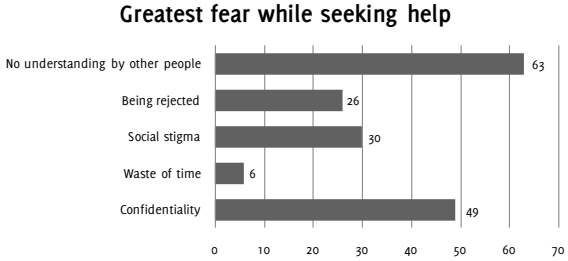


***Figure 2.*** *Acceptability of IEC booklet by study subjects.*

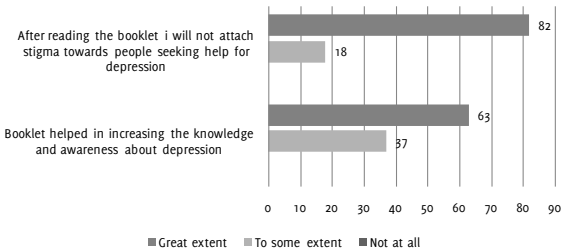


***Table 4.*** *Attitude regarding depression among study subjects.*

| Items | Pre - Intervention (%) | Post - Intervention (%) | Mc Nemar test | p Value |
|---|---|---|---|---|
| Willing to employ recovered person | 79 | 89 | 3.1 | 0.07 |
| Against marrying a recovered person with your close relative | 17 | 24 | 1.09 | 0.20 |
| Comfortable discussing with depressed person | 58 | 73 | 4.1 | 0.04 |

***Acceptability of intervention booklet***

Feedback to determine acceptability of booklet was obtained. As many as 63% students believed that it has increased their knowledge and awareness about depression to a great extent. About 37% felt that it increased their knowledge to some extent. 82% believed that they would not attach stigma towards people with depression seeking help but 18% still thought that they might attach stigma to some extent. The results are displayed in Figure 2.

## Discussion.

Improving knowledge regarding depression needs basic understanding of the students that depression is a disease and needs to be taken care of and not to be left undiagnosed or untreated. Since these issues were addressed in the booklet there was significant improvement in knowledge, attitude and health seeking behavior about depression in students.

The number of students who considered depression a disease increased from 71% to 88%. Most of the students had high knowledge of the causes of depression like neurotransmitter imbalance, abnormal family structure and social circumstances owing to their medical knowledge. But many of them were not aware of factors like poorly nutritive diet, polluted air, and loss of semen or vaginal secretions as causes of depression. This is consistent with findings observed by Kishore et al where it was stated that very small percentage of medical practitioners knew about these causes of mental disorders.[20] It reflects general lack of emphasis on these factors by medical professionals also. The genetic link to depression is an important factor as it helps students to detect depression early in patients with a family history, which was included in the booklet. Few responses in post intervention had gone against the expected finding. For example, there was an increase in the number of students who believed that depression may result due to god punishing them for wrong doing or sins. This could be due to prevalent myths even among medical professionals. Another explanation for this could be that since this intervention was carried out for a short duration only, a person's deep rooted beliefs become stronger in such circumstances. Similar findings of myths and wrong beliefs were reported by Kishore et al.[20] Similar findings on etiology of psychiatric illnesses was reported by a study conducted among medical students by Chawla et al in which excessive emotions, loneliness, past sins and evil spirits were consi-

dered as a cause of psychiatric disorders.[21] It reflects lack of emphasis on these factors in medical teaching as well.

The slight increase in percentage of students who believed that lower socio-economic status increases the risk of developing depression could be due to the fact that they considered lack of resources could result in poorly nutritive diet and polluted housing conditions, which are in turn considered as risk factors for depression. This is consistent with the study carried out among medical professionals in which according to 63% respondents, mental disorders were caused solely by unfavorable social circumstances.[20]

Students were made aware of all the symptoms that could point towards depressive behavior. About 70% students were already aware of the symptoms, which after reading the booklet increased strikingly to 90% in most cases. Identifying these symptoms by the students, which may otherwise appear as general irritable mood swings, for more than 2 weeks in general, can help the students to seek early help. The findings are consistent with the results of a study carried out among Australian medical students in which being sad, down or miserable was stated as a symptom of depression by 71% second year students and 82% of fourth year students. Others symptoms reported were sleep disturbances, being unhappy or depressed, feeling tired all the time, easy fatigability etc.[22]

Most of the students were already aware of the treatment available for depression. There was also a detectable decrease from 43% to 35% in the number of students who believed that depression could be treated by faith healers as well. This is important because it represents that depression is not merely a disease that can be improved by gaining faith but is an abnormal condition with a determinable cause and proper treatment available. However, similar views were expressed by medical professionals regarding faith healer ability to treat mental disorders in another study. In that study 8% of the respondents considered mental illness to be untreatable.[20]

A notable increase from 78% to 94% was detected in number of students who believed that depression can be improved by increasing the awareness of patient towards his feeling. This is important as mostly medical students ward off these feeling as normal emotional response to medical school, so making them aware of their feelings will help them realize that they could be depressed and should seek help. Students need to be made aware of the fact that taking anti-depressant is like taking other medications. The stigma attached to taking anti-depressant medication need to be addressed. After reading the booklet there was a noteworthy fall from 92% to 66% students who believed that taking them had side effects. Side effects involved with them are general side effects but not troublesome enough that the medication can't be taken. It is important to remove misconceptions of students regarding anti-depressants because it could be hindering them to seek help from psychiatric expert.

The attitude of medical students towards depressed individuals was evaluated as it may have repercussions on their future practice and development of intolerance towards depressed individuals. This was also shown by a study conducted among 40 general practitioners (GPs) in Liverpool and Manchester who completed the Depression Attitude Questionnaire (DAQ) and were asked for prescribing information. The ability of GPs to identify depression may not be an independent variable, but may rather reflect other beliefs, attitudes and skills. This has considerable implications for educational interventions in primary care.[23] Hence questions on various issues like employing an individual who has recovered or marriage of a relative with a person having history of depression or the ability to feel comfortable while talking with depressed person were included in the questionnaire.

Considerable improvements were noted in the above questions. However surprisingly, after the study there was a slight increase in number of individuals who would be against marriage to a recovered individual. The basis of this finding could be that after reading the booklet more people became aware of the fact that depression can run in families and thus some preferred not to marry an individual who have recovered from depression. Genetic linkage to depression was told in the booklet, which could be a reason for such attitude.

An important finding was observed in a previous study in the same college that only 4.7% students had ever consulted a counselor even though around 14.7% admitted to have had past depressive episodes.[15] This makes it critical to determine the various aspects of help seeking behavior in students. Most of that students preferred professional counselors (73%) to seek help, this makes counseling an important tool to counteract increasing depression. Similar results were reported by another study where 54% of first year students and 46% of second year medical students preferred counseling.[22] The medium that was mostly favored by students was face-to-face interview (80%). This could be probably due to the ease with which they are able to communicate in the interview, including clarifying their queries.

The main reasons for their not so forthcoming approach in regard to seeking help were also cited. It was found that mostly they felt that nobody could help them (19%) and a few felt ashamed (9%) while seeking help. The main problems faced while seeking help were detected in which no understanding by others was cited as the most common reason (63%) followed by lack of confidentiality of the treatment, fear of documentation of their illness, social stigma (30%) and being rejected by others (26%) and waste

of time (6%) were other reasons. This is consistent with findings of a study conducted in University of California in which the most frequently cited barriers to using these services were determined as lack of time, confidentiality and social stigma.[24] Since social stigma turned out to be a big factor in both the studies, this issue was specifically addressed in the booklet. After reading the booklet, 82% believed that they would not attach stigma but 18% still considered that they might attach stigma to some extent. This can be due to already high prevalence of social stigma in medical students and should be further brought down by counseling. Better interaction with faculty, advisory services and counseling services have been reported to help students to deal with stress and depression according to a study conducted by Shaikh et al in Pakistan Medical School.[25] Thus, knowledge and attitude of students towards depression was found to improve following the educational intervention in the form of IEC booklet.

This is in accord with the fact that most of the students accepted the booklet and 63% found that it increased their knowledge about depression to a great extent and 37% considered that it increased to some extent. The positive feedback obtained is consistent with other studies, which have used other methods of intervention.[26-29]

The study has following limitations: a) the study was confined to only one medical college which limit the generalizability to all medical students. b) Intervention in form of booklet was applied to all students and had no comparative group. Therefore the causal effect of booklet on improvement of knowledge, attitude and practice cannot be stated. c) Long term effect of the booklet could not be assessed.

The study draws conclusion that intervention in the form of booklet had profound improvement in the knowledge of students regarding various aspects of depression such as risk factors, causes, symptoms and treatment. They will attached less stigma to the depression and favorable to work with mentally ill subject. The various myths like antidepressants having a lot of side effects and being addictive were attended to. Thus IEC booklet is effective tool to bring change in their behavior for seeking help for depression if they fall sick.

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**Acknowledgements**
*This project was done as a part of short term studentship received 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.*

**Cite as:**
*Goyal M, Kohli C, Kishore J, Jiloha RC. Effect of an Educational Booklet on Knowledge and Attitude Regarding Major Depressive Disorder in Medical Students in Delhi. Int J Med Students 2013;1(1):16-23.*

IJMS International Journal of Medical Students

Short Communications

# Red Eye: Next Steps for Conducting Research in Knowledge, Attitude and Practice in Ophthalmology

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## Abstract.

**Background:** Research in Knowledge, Attitude and Practice (KAP) in health sciences is relevant to health care providers and patients to identify factors to address educational interventions. **Methods:** A pilot study based on surveys amongst participants in a medical update conference in Cali, Colombia, was conducted to estimate participants' knowledge on red eye in 2011. **Results:** The population was composed of medical students and general practitioners, with 72.7% of students being in their final year of their training. The classification of red eye was correct in 47% of respondents and we found errors in the classification of emergency, glaucoma and uveitis. **Conclusions:** Further research proposals in KAP are required for the recognition of this medical education indicator.

**Keywords:** Health Knowledge, Attitudes, Practice; Eye Hemorrhage; Students, Medical (Source: MeSH, NLM).

## Introduction.

A study of knowledge, attitudes and practices (KAP) has been widely used in community medicine and in some clinical areas, an annual increase of publications in the area in the past 10 years, illustrating its importance.[1]

The relevance of KAP studies lies in the possibility of the researcher to recognize, measure and establish the extent of knowledge on a specific topic in a population. It's commonly used as a tool to provide an educational diagnosis of health staff on diseases and their medical or surgical management, enabling to design interventions for improving the care of patients, and in medical education.[2]

It is striking the lack of these studies in ophthalmology as evidenced in MEDLINE by searching PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez) using the term "Health Knowledge, Attitudes, Practice"[Mesh] appear as result 58,163 articles, but adding the term "Ophthalmology" ("ophthalmology"[Mesh] AND "Health Knowledge, Attitudes, Practice"[Mesh]) appear a total of 55 (0.094%), of which 13 do not correspond to KAP studies in ophthalmology, leaving 42 (0.072%) articles in total, of which 15 (35.7%) assessed patients, 20 (47.6%) ophthalmologists, 3 (7.1%) general practitioners, 3 (7.1%) medical students and 1 (2.3%) tested two populations: ophthalmologists and patients.

From this information grew the initiative to propose a pilot study based on a self-administered questionnaire assessing basic knowledge in a frequent ocular sign in general practice, the red eye; listed as the leading cause of eye consultation to the general practitioner in primary care.[3]

Red eye is the most common and nonspecific ocular sign encountered in emergency and outpatient settings. The term red eye might represent infectious and inflammatory conditions involving one or more ocular tissues, including the conjunctiva, cornea, lids, and internal ocular structures.[3]

This symptom accounts for approximately 15% of consultations for ophthalmologists and 6% for general medical practitioners.[4] Red eye is the most common ocular symptom seen by primary care physicians[5] and therefore the knowledge, attitudes and practices is important to guide the patient management and improve the visual prognosis of patients. The causes of red eye are show in Table 1.

The objective of this study was to establish the Knowledge in red eye, of participants in a medical update conference in Cali, Colombia.

## Methods.

A pilot study based on surveys with a self-administered questionnaire amongst participants in a medical update conference in Cali, Colombia, was conducted in order to estimate knowledge on the approach to red eye and its

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*Submission: 2012, April 30.*
*Accepted: 2012, Jul 11.*
*Process: Peer-Reviewed.*

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differential diagnosis. The survey consisted of five multiple choice questions with a single correct answer, evaluating the following topics: classification of red eye, clinical presentation of acute angle closure glaucoma, conjunctivitis and uveitis, and the recognition of an ophthalmologic emergency. The survey counted with the review and approval of 2 experts in the field.

The study population was the participants attending a medical update conference held in the Cali, Colombia in September 2011, which involved 202 individuals, who were medical students and general practitioners.

The study is considered of "minimal risk" as there is no intervention and the individual's identity is kept anonymous, fulfilling the ethical standards issued by the Nuremberg Code and the Declaration of Helsinki on research in humans.

The surveys were collected and typed in a database designed for this purpose in Microsoft Office Access®, and we searched for typing errors by evaluating 20% of the surveys. Data analysis consisted on a frequency analysis with statistical software Stata 12®, presenting quantitative variables with means and standard deviation (SD), and categorical variables in frequencies and percentages.

## Results.

Two hundred and two surveys were distributed to the participants. The response rate was 32.7% (66).

Among people who completed the survey, 26 (39.39%) were female and 40 (60.61%) were men. The ages of participants was in the range of 18 to 37 years with a mean of 23.6 (SD ± 3.7). Eighty percent (53) of responders were in the range of 18 to 25 years and 19.7% (13) were between 26 to 37 years.

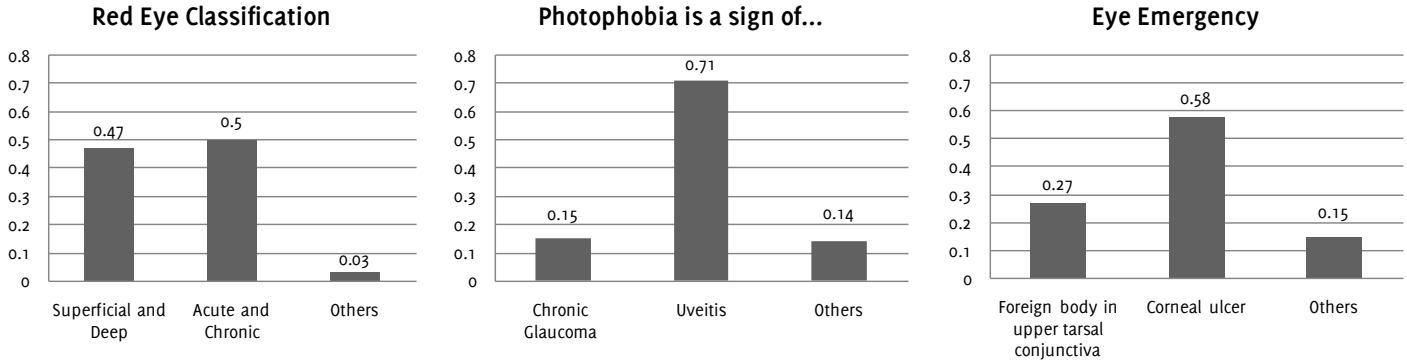
The participants were from universities or medical institutions, with a total of 11 (16.67%) general practitioners and 55 (83.3%) medical students from 9 different universities.

***Table 1.*** *Common causes of red eye. Adapted from Seth (3).*

| |
|---|
| **Conjunctiva** |
| Infectious conjunctivitis |
| Neonatal |
| Post-neonatal |
| Chemicals and irritants |
| Allergic conjunctivitis |
| Subconjunctival hemorrhage |
| **Trauma** |
| Corneal abrasion |
| Foreign body |
| Hemorrhage |
| Burns |
| Blunt or penetrating injury |
| Contact lens problems |
| Child abuse |
| **Lid** |
| Hordeolum |
| Blepharitis |
| Chalazion |
| **Nasolacrimal duct** |
| Dacryostenosis |
| Dacryocystitis |
| **Preseptal and orbital cellulitis** |
| **Cornea** |
| Corneal ulcer/abrasion |
| Keratitis |
| **Uveitis** |
| **Allergic reactions** |
| **Angle closure glaucoma** |

We found that, 25 (37.88%) persons were in their 5th year of medical school of a 6-year program, 13 (19.7%) final year medical students, 11 (16.67%) general practitioners, 10 (15.15%) in 4th year of medical school, 6 (9.09%) in 3rd

***Figure 1.*** *Distribution of survey responses about knowledge in red eye classification, photophobia sign/symptom, and eye emergency, of participants in a medical update congress in Cali, Colombia.*



year, and 1 (1.52%) person in 1st year of medical school. Majority of the universities in the country were represented by medical students in their final years (4th to 6th), with percentages of students at this academic level in each university ranging from 50 to 100%.

The correct answers were distributed as follows: in the classification of red eye 47% (31), in the clinical presentation of acute angle closure glaucoma 95.5% (63), in the case of conjunctivitis 93.9% (62), in uveitis 71.2% (47), and in recognition of an ophthalmological emergency 57.6% (38) of participants gave a correct answer.

Additionally we found wrong concepts in some answers (Figure 1): In the classification of red eye, the 50% (33) of the participants chose the acute and chronic classification. About the clinical presentation of uveitis, 28.7% (19) of the participants answered incorrectly and the most frequent mistake was diagnosing chronic glaucoma (open angle glaucoma) with a 15.1% (10). Finally, about an ocular emergency, 57.6% (44) of participants answered incorrectly, and 27.3% (18) considered a retained foreign body in upper tarsal conjunctiva as an emergency.

## Discussion.

The Knowledge possessed by a community refers to their understanding of that topic. Attitude refers to their feelings toward this subject, as well as any preconceived ideas they may have towards it. Practice refers to the ways in which they demonstrate their knowledge and attitudes through their actions.[2]

To consider the red eye as a sign should be the first teaching for medical students in their approximation to ophthalmology, but this is usually neglected because the practice in this area is inadequate; in Colombia for example, the regular rotation in most universities lasts only two weeks.

Probably the red eye is not the most common consultation in general practice but when the physician is exposed to it, he should be able to provide a differential diagnosis and propose a management plan or at least determine emergency situation from non-emergency referral.[4]

The pathophysiology of the red eye relies in the ocular anatomy and physiology. The vasculature of the eye is comprised of a superficial and deep layers, the first nurturing the conjunctiva and episclera, and the second the choroid and retina, therefore a problem in these vasculatures anywhere in the eye will produce a red eye,[6] for this reason it is not a diagnosis, it is a sign, and the challenge lies in identifying the precise diagnosis.

The history plays a fundamental role in the diagnosis of a disease manifested with red eye, and the visual acuity needs to be evaluated as it is the key to provide an accurate initial assessment and differential diagnosis.[4,6]

The co-findings of red eye are multiple and include redness, epiphora, pain, photophobia, itching, and visual acuity alteration. Recognition of situations when a red eye constitutes an emergency is fundamental in the primary care setting for the initial treatment and referral of the indicated patients, preventing the possibilities of permanent loss of vision.[3-4,6]

The main indication for referral of patients to an ophthalmologist are: vision loss, purulent discharge, corneal edema, opacities and staining with fluorecein, history of trauma with anatomical distortion, or distorted pupil.[3] Other authors also suggest that if the symptoms are severe or rapidly progressive, urgent referral to an ophthalmologist is appropriate.[6]

Petricek et al.,[4] conducted a survey to estimate the percentage of patients presenting with red eye and to examine differential diagnosis and treatment amongst general practitioners and ophthalmologists from 9 countries in Eastern Europe and the Middle East. They found that patients presented with chief complaint of red eye in 15% of the ophthalmologist practice and 6% of general practitioners. Diagnosis of allergic conjunctivitis was the most common cause of red eye (35%), followed by dry eyes (25%) and bacterial conjunctivitis (24%), and the general practitioners were more likely to prescribe combinations of topical antibiotic and steroids.

In this pilot study it is concerning that a significant percentage of medical students in their final years of medical education are unclear of the real causes of ocular urgencies. It's important to evaluate the medical education in ophthalmology because the general practitioners are who have the first possibility to direct the management of an urgent case, which will impact the visual prognosis.[4]

Further studies on KAP in ophthalmology are required, since they account for 0.07% of the articles published in this topic in PubMed, and this report found errors in the evaluated population in the classification of diseases where the main symptom is red eye. The authors propose further investigation in KAP in red eye and other eye diseases is needed, to improve medical education and the patient management.

This study has limitations in sample size and sample selection, and in administering the same questionnaire to people in different stages of their training, but the assessment results and the small number of publications in KAP in ophthalmology, are an incentive and serves to encourage the implementation of further research about KAP in ophthalmology and to highlight the importance of such investigations.

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**Conflict of Interest Statement & Funding**

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

**Cite as:**

*Bonilla-Escobar FJ, Ocampo-Dominguez HH. Red Eye: Next Steps for Conducting Research in Knowledge, Attitude and Practice in Ophthalmology. Int J Med Students 2013;1(1):24-7.*

IJMS International Journal of Medical Students

Reviews

# Real-Time Polymerase Chain Reaction: Applications in Diagnostic Microbiology

Kordo B. A. Saeed[1], Nusreen S. Ahmad[2].

## Abstract.

The polymerase chain reaction (PCR) has revolutionized the detection of DNA and RNA. Real-Time PCR (RT-PCR) is becoming the gold standard test for accurate, sensitive and fast diagnosis for a large range of infectious agents. Benefits of this procedure over conventional methods for measuring RNA include its sensitivity, high throughout and quantification. RT-PCR assays have advanced the diagnostic abilities of clinical laboratories particularly microbiology and infectious diseases. In this review we would like to briefly discuss RT-PCR in diagnostic microbiology laboratory, beginning with a general introduction to RT-PCR and its principles, setting up an RT-PCR, including multiplex systems and the avoidance and remediation of contamination issues. A segment of the review would be devoted to the application of RT-PCR in clinical practice concentrating on its role in the diagnosis and treatment of infectious diseases.

**Keywords:** Real-Time Polymerase Chain Reaction; Reagent Kits, Diagnostic; Molecular Diagnostic Techniques (Source: MeSH, NLM).

## Introduction.

Polymerase chain reaction (PCR) is a molecular based technique. It derives its name from one of its key components, DNA polymerase, which is used to amplify a piece of DNA by in vitro enzyme-mediated replication. As PCR progresses, the DNA thus generated is itself used as template for replication. This in turn will set in motion a chain reaction in which the DNA template is exponentially amplified. The technique can be used to amplify single or few genomic copies of a target, which would otherwise remain undetected. A key component for this process is a pair of primers, which are composed of oligonucleotides (about 20 nucleotides in length); these are complementary to a pre-defined sequence on both the forward and reverse strands of DNA. The same primers can be used again and again, to make other copies of the target sequence. A revolutionary step in the process was the discovery of a thermo-stable DNA polymerase, Taq polymerase, from *Thermophilus aquaticus* a bacterium that can withstand extreme temperatures, allowing the reaction to continue without the addition new polymerase in every round of the process. For conventional PCR, 35 cycles of amplification are usually carried out, and the product can be visualized in the form of "bands" on agarose gel. This is a qualitative approach, as often the amount of product is not related to the amount of input DNA.

Real time-PCR (RT-PCR), a technique that follows the general basics of conventional PCR however it allows the measurement of PCR products in real time as the reaction progresses. Reverse transcriptase PCR analysis of RNA, which can also mistakenly be abbreviated as "RT-PCR", is an analysis to measure RNA. Here RNA is copied to complementary DNA (cDNA) by reverse transcriptase. This product the is amplified by PCR allowing the formation of a second strand of DNA, which can be further amplified and eventually analyzed conventionally or in real time. In this review the abbreviation RT-PCR represents real-time PCR.

## Processes and Principles of RT-PCR.

### *Nucleic acid extraction processes*

There are many different commercial platforms available for nucleic acid extraction. The choice of extraction platform will depend on the needs of the laboratory in terms of the quantity of samples received. Low, medium and high throughput automated extraction platforms can be widely found from most companies, which can be used to process up to 96 samples in one extraction run. In most cases the chemistry for RNA (as RNA is less stable, reagents are added to stabilize the extracted nucleic acid) and DNA extraction will differ but the extraction process will remain the same.

*Submission: 2011, Dec 15.*
*Accepted: 2012, Feb 19.*
*Process: Peer-Reviewed.*

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The extraction process usually begins by lysing the cells of the target organism using enzymes such as proteinase K. Once lysed, the nucleic acid can then be bound to a membrane or to glass beads which are then washed several times to remove any possible inhibitors that may be present in the original sample and the remaining enzymes used for lysis. Once washing is complete, the nucleic acid can then be eluted off in to a clean collection tube. This extract is then ready for PCR. At this stage the eluate can be stored at -20°C for a short period of time if PCR is not planned immediately. Manual extraction processes also follow the same format of lysing, binding, washing and eluting.[1-3]

***Principles of RT-PCR***

As with conventional PCR, in RT-PCR, double strand DNA (ds-DNA) is denatured at approximately 95°C, this high temperature breaks the hydrogen bonds that bind one side of the helix to the other allowing the two strands separate. The sample is cooled to between 50 to 60°C to allow annealing of primers that are complementary to a specific site on each strand. The temperature is raised to 72°C and the addition of the heat-stable Taq polymerase extends the DNA from the primers generating four cDNA strands. A major improvement in this system is the addition of a dual labeled probe, which contains a flurophor on one end and a quencher molecule on the other. The shape of the un-bound probe allows the flurophor and quencher molecules to sit in close proximity to each other preventing the premature release of fluorescence. After each cycle, the level of fluorescence released is measured when bound to the ds-DNA i.e. the PCR product. The progress of PCR amplification can be continuously monitored in real time by acquiring fluorescence signals in each amplification reaction cycle. Thus, after 30 to 40 cycles, quantitative information of the PCR process is obtained by plotting the intensity of the fluorescence signal versus cycle number (Figure 1 and 2). Automated assays are relatively easy to perform and they are not only valuable in reducing chances of contamination, but also enable reproducibility and rapid processing of multiple samples

Duplex, triplex and multiplex RT-PCRs are reactions in which two, three or more fluorogenic probes are used simultaneously for the discrimination of multiple amplicons in a single tube. These reactions are possible because probes labeled with fluorescent dyes with different excitation and emission spectra allowing each target to me measured independently of the others. The main advantages of multiplexing over single-target analysis are the ability to provide internal controls, lower reagent costs and preservation of precious samples. The introduction of combinatorial fluorescence energy transfer tags is important in boosting the development of multiplex real-time PCR.[4]

There are two quantifications types from RT-PCR,[5-7] one of which is an absolute quantification that requires an input standard curve with series diluted template (five- or tenfold serial dilution). This curve is used as a reference standard for extrapolating quantitative information for target nucleic acid. Using the known copy level of the standard reagent, the software of the PCR instrument generates a standard curve in a plot that relates fluorescence (measure of amplified product) and the cycle number in which the nucleic acid target is detected. This method determines the absolute amount of a target (expressed as copy number or concentration), which is one of the most accurate standards for gene expression analysis.

***Figure 1.*** *The principle of RT-PCR with dual labeled probe containing a flurophor on one end and a quencher molecule on the other.*

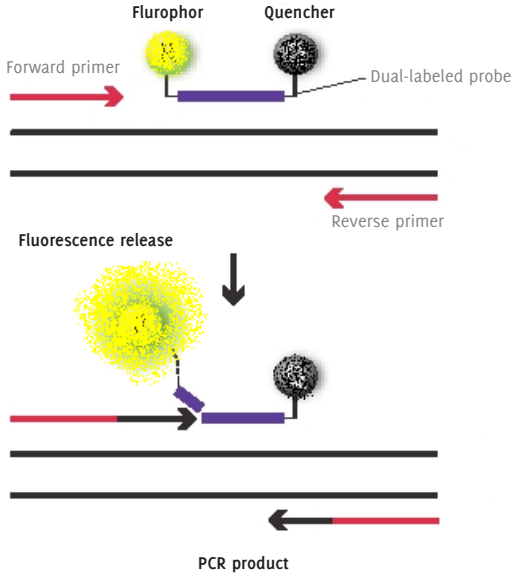
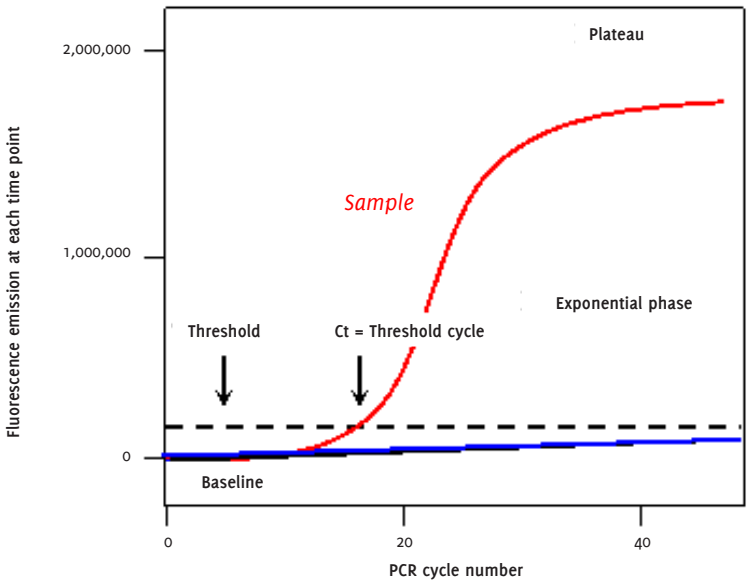



***Figure 2.*** *Graphic representation of RT-PCR quantitative plot after 40 cycles, quantitative information of the PCR process is obtained by plotting the intensity of the fluorescence signal versus cycle number.*



Relative quantification, also known as the comparative threshold Method determines the ratio between the amount of target and an endogenous reference gene, usually a suitable housekeeping gene, that are not expected to change under the experimental conditions serve as a convenient internal standard. This normalized value can then be used to compare, for example, differential gene expression in different samples. The target and the reference genes are amplified from the same sample, either separately or in the same reaction (duplex RT-PCR). The normalized value is determined for each sample and can be used to compare, for example, differential expression of a gene in different tissues. Because the absolute quantity of the internal standard is not known, only relative changes can be determined by this method. If a housekeeping gene cannot be found whose amplification efficiency is similar to the target, then the standard curve method should be used.

## Chemistries, Instrumentations, Designs and Reagents of RT-PCR.

***Chemistries of RT-PCR***

The key to real-time PCR is the ability to monitor amplification as it occurs. This is accomplished by specific chemistries and instrumentation. Generally, chemistries consist of special fluorescent probes in the PCR. Several types of probes exist, including DNA-binding dyes like SYBR green I which intercalate in to the ds-DNA as it is formed, hydrolysis probes (5_-nuclease probes), hybridization probes, molecular beacons, sunrise and scorpion primers, and peptide nucleic acid (PNA) light-up probes. Each type of probe has its own unique characteristics, but the strategy is they must link a change in fluorescence to amplification of DNA.

One class of RT-PCR chemistry uses different fluorescent dyes incorporated in short oligonucleotide probes specific for the amplified target. Another class consists of dyes that bind ds-DNA and become fluorescent; the most commonly used of these is SYBR Green I.[8] SYBR Green I fluorescence is enormously increased upon binding to the minor groove ds-DNA. As it is an intercalating fluorescent dye, during the extension phase, more and more SYBR Green I will bind to the PCR product, resulting in an exponential rise on fluorescence. Consequently, during each subsequent PCR cycle more fluorescence signal will be detected. The technique is inexpensive and generic, as it requires the same detection reagent for each template to be tested. But detection with dyes like SYBR Green I are less specific than probe-based detection methods. In addition, SYBR Green I cannot be used in multiplexed assays. The benefit of using this type of assay in a non clinical setting is to investigate the possibility of contamination during the validation process. This method can be used to visualize the melting temperatures of various targets that may have been inadvertently introduced in to the PCR mix as they are likely to have a different melting temperature to the actual target in question. This process can replace the laborious task of pouring and running conventional gels to look for contamination. It is worth noting that SYBR Green is not commonly used in routine clinical practice.

Hydrolysis probe technique: Addressing the specificity problem, these are sequence-specific and conjugated with a quencher fluorochrome, which absorbs the fluorescence of the reporter fluorochrome on condition that the probe is intact. However, upon amplification of the target sequence, the hydrolysis probe is displaced and subsequently hydrolyzed by the Taq polymerase. This results in the separation of the reporter and quencher fluorochrome and consequently the fluorescence of the reporter fluorochrome becomes detectable. Throughout the PCR cycles this fluorescence will further increase because of the progressive and exponential buildup of free reporter fluorochromes.[1] This allows results to be visualized in real-time which in a clinical setting can be important.

TaqMan probes depend on the 5'- nuclease activity of the DNA polymerase used for PCR to hydrolyze an oligonucleotide that is hybridized to the target amplicon. The probe has a fluorescent reporter dye attached to its 5´ end and a quencher dye at its 3´ terminus. If the target sequence is present, the fluorogenic probe anneals downstream from one of the primer sites and is cleaved by the 5´ nuclease activity of the Taq polymerase enzyme during the extension phase of the PCR. Whilst the probe is intact, fluorescence resonance energy transfer (FRET) occurs and the fluorescence emission of the reporter dye is absorbed by the quenching dye. During PCR, when the polymerase replicates a template on which a TaqMan probe is bound, the 5'- nuclease activity of the polymerase cleaves the probe. This separates the reporter and quencher dyes, thereby increasing the fluorescence from the former, which has a linear relationship with the amount of probe cleavage. Well-designed TaqMan probes require very little optimization, and can be used for multiplex assays. There are several other variations on the reporter-quencher theme, including molecular Beacons, sunrise primers, and scorpion primers. It is possible to convert a monoplex assay in to a sequence of multiplex assays allowing more than one target to be identified in one single reaction. This is important in a clinical setting especially when dealing with samples such as cerebrospinal fluid which are difficult to collect and often come in small volumes. Each extraction may only elute as little as 50µl so being the ability to test multiple targets whilst using the minimal amount of eluted nucleic acid is an advantage.

Hybridization probes technique: In this technique one probe is labelled with a donor fluorochrome at the 3' end and a second –adjacent- probe is labeled with an acceptor fluorochrome. When the two fluorochromes are in close vicinity (1–5 nucleotides apart), the emitted light of the donor fluorochrome will excite the acceptor fluorochrome FRET. This

results in the emission of fluorescence, which subsequently can be detected during the annealing phase and first part of the extension phase of the PCR reaction. After each subsequent PCR cycle more hybridization probes can anneal, resulting in higher fluorescence signals. This method is widely been used for detection of minimal residual disease after treatment and viral load quantification.[1]

***Instrumentation of RT-PCR***

The chemistries and instrumentation of RT-PCR are closely connected. The instrumentations that are required for RT-PCR technique consists of a thermal cycler for amplification, a light source for excitation of fluorescent probes, a camera for recording, and a computer to control instruments and record data. Because fluorescent chemistries require both a specific input of energy for excitation and a detection of a particular emission wavelength, the instrumentation must be able to do both simultaneously and at the desired wavelengths. Scientists can be faced with a daunting task when selecting platforms as machines are available from several manufacturers, with difference in sample capacity (e.g. 96-well standard format, some require specialized glass capillary tubes), methods of excitation, some use lamp (broad-spectrum emission devices), light-emitting diode (LED), or laser (narrow spectrum), and overall sensitivity. There are also platform-specific differences in how the software processes data. Emission energies must also be detected, by cameras or other types of photodetectors, at the appropriate wavelengths in order to collect appropriate data. Narrow wavelength filters or channels are generally employed to allow only the desired wavelength(s) to pass to the photodetector to be measured. The detector and the capability of the instrument for distinguishing different wavelength signals can influence the level of assay and allows for multiplexing.

Efficient performance of quantitative PCR requires rapid, precise, thermal control. Hence, the significance of the thermocycler in RT-PCR is in its ability to maintain a consistent temperature among all sample wells, as any differences in temperature could lead to erroneous PCR amplification efficiencies. The temperature uniformity has a direct impact on the ability to discriminate between different PCR products by performing melting point analysis. Additionally, the resolution with which instruments are able to control temperature is a major factor, which affects their performance when performing high resolution melting analysis. Thermal non-uniformity during temperature cycling contributes to variability in PCR and can affect the RT-PCR accuracy. This can be solved by using a heating block, heated air, or a combination of the two. It is important to ask respective manufacturers to provide up to date information on the platform you chose to purchase for your facility. To ensure consistent analysis and reporting of results, suitable computer hardware, data-acquisition and analysis software are essential to complete the process.[9]

***Design of RT-PCR Assays and reagents used***

PCR cannot take place without a number of specific reagents, that include;

- DNA template that contains the DNA region (target) to be amplified.
- Two primers, which are complementary to the DNA regions at the 5′ (five prime) or 3′ (three prime) ends of the DNA region.
- DNA or Taq polymerase.
- Deoxynucleoside triphosphates (dNTPs; also very commonly and erroneously called deoxynucleotide triphosphates), the building blocks from which the DNA polymerases synthesizes a new DNA strand.
- Buffer solution, providing a suitable chemical environment for optimum activity and stability of the DNA polymerase.
- Divalent cations, magnesium or manganese ions; generally $Mg^{2+}$ is used, but $Mn^{2+}$ can be utilized for PCR-mediated DNA mutagenesis, as higher $Mn^{2+}$ concentration increases the error rate during DNA synthesis.
- Monovalent cation potassium ions.

The PCR is commonly carried out in a reaction volume of 20-150 µl in small reaction tubes (0.2-0.5 ml volumes) in a thermal cycler. The thermal cycler heats and cools the reaction tubes to achieve the temperatures required at each step of the reaction (see below). Many modern thermal cyclers make use of the Peltier effect which permits both heating and cooling of the block holding the PCR tubes simply by reversing the electric current. Thin-walled reaction tubes permit favorable thermal conductivity to allow for rapid thermal equilibration. Most thermal cyclers have heated lids to prevent condensation at the top of the reaction tube. The efficacy of RT-PCR is determined by its specificity, low background fluorescence, steep fluorescence increase, high amplification efficiency, and high level plateau.[10-13]

## Contamination Prevention and Control in the PCR Laboratory.

Contamination remains an issue for laboratories performing detection of microbes using PCR. RT-PCR processing can be classified into two major groups, the pre-PCR stage (including preparation of both the sample and PCR reagents) and post-PCR (PCR execution and analysis). Compliance with guidelines to prevent contamination is essential for successfully operating a PCR laboratory on a long-term basis. Guidelines must be part of a network of protocols or standard operating procedures focused on maintaining a contamination- free zone in the laboratory. Contamination sources vary, e.g. one of the most frequent causes of PCR product contamination is the generation of aerosols of PCR amplicons that is associated with the post-PCR analysis. Other sources include previous procedures and amplified molecules (“amplicons”). Purification of plasmid clones, repeated isolation of template nucleic acids should not be ignored as potential sources; DNA templates are typically

more troublesome as contaminants because they are more stable than RNA targets. There are a number of approaches to control of PCR contamination, and the stringency that is required in a laboratory is invariably determined by the assay being performed. A practical approach to control contamination is to segregate activities and limit the performance of PCR activities to its own area. The crucial steps in preventing, eliminating or controlling contamination include separation of pre- and post-PCR procedures, utilization of physical barrier approaches e.g. maintaining a unidirectional flow of work in the laboratory, the use of barrier pipette tips to prevent aerosols generation, or use of chemical means e.g. use of ultraviolet photolinking, use of aliquoted PCR reagents, incorporation of numerous positive and negative or blank PCRs ($H_2O$ substituted for template), and use of Uracil-DNA-glycosylase (UDG) an enzyme effective at destroying PCR amplicons when vigorously used for sample preparation. Use of consistent, careful technique by the operator coupled with monitoring of PCR controls will ensure a proactive approach to PCR contamination.

## Troubleshooting in RT-PCR.

***Poor PCR amplification efficiency with little or no PCR product***

This can often be caused by poor quality oligonucleotides, a badly extracted sample (resulting in poor quality template), insufficient sample (where the nucleic acid may be too diluted to be detected) or by expired or poor quality reagents that are not suitable for the RT-PCR platform. It is necessary to include both positive and negative controls as well as an extracted internal positive control in order to determine both the extraction efficiency and the presence of inhibitors in the sample and the efficiency of the PCR.

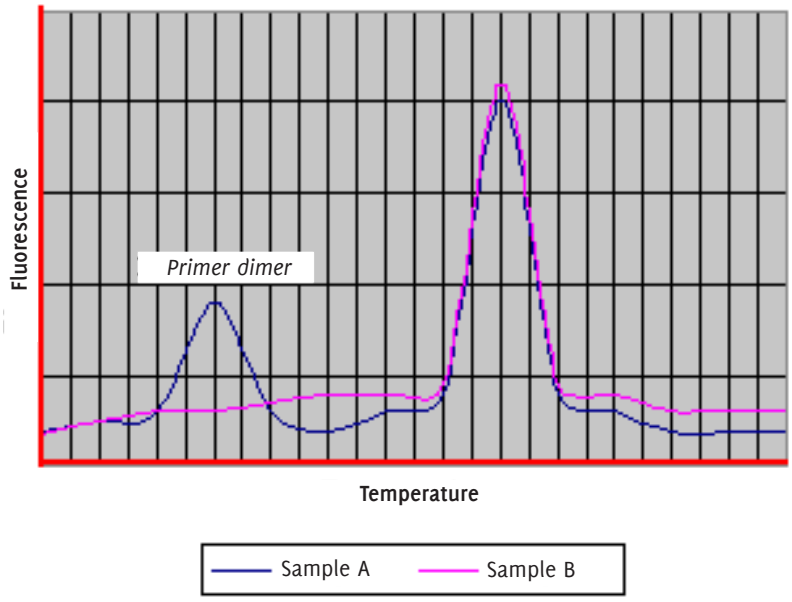
***Primer dimers***

Can be observed when gene expression is low and can be easily resolved by increasing concentration of the target template. Primers that have been designed to be less than 24 base pairs long and which are not rich in "GC" content, ensuring that there are no more than three "G's" together and also preventing the use of "G" oligonucleotides at the 5' end often will help to prevent the formation of primer dimers (Figure 3).

***Non-specific amplicons, multiple bands or multiple peaks in the melting curve***

The presence of spurious bands in both melt curve analysis and agarose gel electrophoresis is most likely to occur due to poor assay optimisation. In this case it is advisable to investigate further both the cycling conditions (non specific binding can occur if the annealing/extension temperature in a "two step" PCR is far lower than the combined melting temperature of both the primers and probe) and chemistry of the assay. It is also necessary to "check" the oligonucleotide sequences to ensure that those selected are common only to the target organism.

***Figure 3.*** *Primer dimer can be observed in RT-PCR when gene expression is low and can be easily resolved by increasing concentration of the target template.*




## Advantages and Limitations of RT-PCR .

RT-PCR has the ability to quantify nucleic acids over a wide dynamic range (7-8 log units). This is coupled to high technical sensitivity, allowing the detection of less than five copies of a target sequence. With appropriate internal standards and calculations, mean variation coefficients are 1–2%, allowing reproducibility. In addition, all real-time platforms are relatively quick, with some affording high-throughput automation. RT-PCR is performed in a closed reaction vessel that requires no post-PCR manipulations, thereby minimizing the chances for cross contamination in the laboratory.

Like other diagnostics there are several limitations to RT-PCR methods. RT-PCR is susceptible to inhibition by compounds present in certain biological samples. Because of the necessary use of RNA in an extra enzymatic step, errors can occur. RNA itself is extremely labile compared with DNA, and therefore isolation must be carefully performed to ensure both the integrity of the RNA itself and the removal of contaminating nucleases, genomic DNA, and reverse transcriptase or PCR inhibitors. This can be a problem with any sample source, but clinical samples are of special concern because inconsistencies in sample size, collection, storage, and transport can lead to a variable quality of RNA templates. Conversion of RNA to cDNA during the RT reaction is also subject to variability because multiple reverse transcriptase enzymes with different characteristics exist, and different classes of oligonucleotides can be used to prime RT.

Probably the largest present limitation of RT-PCR, however, is not inherent in the technology but rather resides in

human error: improper assay development, incorrect data analysis, or unwarranted conclusions. RT-PCR primer sets must be designed and validated by stringent criteria to ensure specificity and accuracy of the results. For microbiology, false positives or negatives must be considered when designing an assay to detect pathogens. Amplification and melting curves must be visually inspected while independent calculations based on these curves should be double-checked for accuracy. Of course, conclusions based on data derived from RT-PCR are best utilized when the biological context is well understood.

## Applications of RT-PCR in a Diagnostic Microbiology Laboratory.

RT-PCR is widely used across many clinical disciplines for example in clinical oncology RT-PCR has been used for the detection and quantification of chromosomal translocations, to monitor minimal residual disease or to show graft-versus lymphoma effects.[14-16] Other applications include predictive genetic testing and the identification of relevant single nucleotide polymorphisms. Another major area for applications of real-time reverse transcriptase RT-PCR assays is the quantification of gene expression.

In this section we would like to concentrate on the application of RT-PCR in clinical microbiology where highly conserved regions of the target organism genome tend to be chosen for assay development to avoid detection failure especially in agents with high mutation rates. The concern is with the emerging infectious agents e.g. severe acute respiratory syndrome coronavirus (SARS-CoV), where comparative genome investigations should be performed before a reliable assay can be developed.[1,17,18]

### *Bacteria*

Results of RT-PCR assays for detection bacteria can inform the clinician of the infection status of the patient more rapidly than culture methods. This is of particular importance as in the current era of rising antimicrobial resistance; it allows more specific and timely administration of appropriate and directed antimicrobial therapy. This will not only increase the treatment efficiency but also reduce the time of hospitalization, and avoid the inappropriate use of antibiotics with unwanted effects.

PCR has long been the preferred method for diagnosis of bacteria that are difficult to culture, and numerous RT-PCR assays have already been developed to replace conventional PCR methods for bacteria such as *Legionella pneumophila* (which can take up to fourteen days for cultures to grow), Chlamydiophilia (which can only be cultured in active tissue cell lines) and *Mycobacterium spp* (can take weeks to grow). The method has now become an important tool in the rapid detection bacterial pathogens implicated as biological weapons. An excellent example is the successful application of RT-PCR for screening for the presence of Bacillus anthracis spores and for differentiation based on virulence encoding plasmids and chromosomal markers.
Some RT-PCR assays may also be useful in deciding on the use of antimicrobial agents. The rapid turnaround time of RT-PCR can detect and monitor the antibiotic resistance of clinical isolates of bacteria such as, enterobacteriacae (e.g. Extended spectrum Beta lactamse producers ESBL or Metallo Beta lactamse producers), *Staphylococcus aureus*, *S. epidermidis*, *Helicobacter pylori*, *Enterococcus faecalis*, and *Enterococcus faecium* (Glycopeptide resistant enterococci or GRE or VRE). For example, rapid RT-PCR analysis detecting rifampin resistance in *M. tuberculosis* complex, and a RT-PCR was applied successfully to screen for MRSA from nasal swabs and joint fluids.[19,20] RT-PCR is becoming one of the main tests proposed for multi-step algorithms in testing for *Clostridium difficile* genes in suspected cases with negative immuno-assays.[21] Another important area is the ability to extract *E. coli* 0157:H7 DNA, directly from stool specimens, which is not only important for patient management but also for prompt epidemiological investigations. A specific PCR for detecting *Neisseria meningitides*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* has provided more rapid results than culture, especially where antibiotics are administered before samples were obtained.[22]

RT-PCR can complement histopathological and serological analysis, e.g. detection of *Bartonella henselae*, a difficult to culture organism, in patient samples with suspected Cat Scratch Disease. As is the case for other fastidious organisms, PCR offers an attractive alternative for detecting *Bordetella pertussis* and *B. parapertussis* in clinical specimens. PCR can be used to detect *Tropheryma whipplei* genes from a variety of human specimens, allowing appropriate treatment with antibiotics for appropriate duration. Further more, the laboratory diagnosis and screening for *Borrelia burgdorferi* (Lyme borreliosis) is currently based on serology which has some drawbacks e.g. false negatives mainly during the early stages of the infection and false positive results especially in some patients with autoimmune disease. PCR on various tissues and body fluids, including the CSF, may have the potential to be helpful to tackle these issues, however, details of patient sample requirements and rapid sample preparation techniques remain to be worked out.[23-26]

### *Viruses*

Since its discovery, RT-PCR has had a major impact on clinical virology. This is mainly due to the less genetic complexity of these organisms, the lack of rigid cell membranes makes it easier to extract nucleic acids from viruses and traditionally the effort of conventional culture is great for viruses.

Qualitative Viral Assays have been applied in the diagnosis of Herpes simplex virus (HSV), data has shown increased detection rates by RT-PCR for up to 300% over cell culture methods for diagnosis of HSV infections, with faster tur-

naround times at equivalent cost.[27] Varicella-zoster virus (VZV): RT-PCR techniques permit highly sensitive same-day detection of VZV in clinical specimens, e.g. in testing CSF samples for the diagnosis of VZV meningitis or encephalitis. Enteroviruses: Collectively, these viruses are associated with diverse clinical manifestations ranging from mild febrile illness to aseptic meningitis, encephalitis, myocarditis, and poliomyelitis.

Early detection of these agents in clinical samples have shown valuable in reducing medical costs incurred by patients by reducing hospitalization and hospital stays and the use of unnecessary antibiotics and antiviral agents.[28] Other applications are in the diagnosis of respiratory Viruses, including Adenovirus, Influenza virus types A and B, Parainfluenza virus, Respiratory syncytial virus (RSV), SARS-CoV and Human Metapneumovirus. Rapid laboratory diagnosis of influenza is critical for infection control, especially in hospital and nursing home settings intervention with effective antiviral treatment if provided to the patient in the early stages of this viral disease.

Conventional techniques e.g. cell cultures, are hazardous in some cases e.g. SARS-CoV, because of the risk of laboratory-acquired infections with this agent and bio-safety level 3 laboratory facilities are required for culturing the virus Commercial RT-PCR reagents are critical not only for the rapid recovery and identification of SARS-CoV, but also for reducing transmission to healthcare workers and laboratory personnel. RT-PCR using throat or nasopharyngeal samples also played a major role in early diagnosis during the 2009-10 "pandemic" of H1N1 or "swine flu". These tests have improved the capabilities of hospital and public health laboratories for diagnosing viral respiratory tract infections and emerging infections and assisted public health agencies in identifying outbreaks and pandemics.[29-31]

Quantitative Viral Assays have been used to assess the relationship between the viral load (copy level) and the prediction of progression of infection and development of clinical disease. For example in Cytomegalovirus (CMV) using serial samples from transplant cases to monitor CMV DNA/ml, by RT-PCR, have been used to detect evolving symptomatic infection or for initiating preemptive antiviral therapy. Similarly quantification of Epstein-Barr Virus (EBV) DNA provides the potential for the designation of viral load levels generally associated with healthy or subclinical carriers of EBV (reactivated infection) compared with those levels of virus that produce disease states such as post transplant lymphoproliferative disorder in transplant patients.[32,33]

Human Immunodeficiency Virus (HIV): HIV-1 and HIV-2 RNA levels in the plasma of infected individuals can be determined reliably by quantitative rapid RT-PCR assays. These assays will help clinicians in early identification of patients who are virologically responding to highly-active antiretroviral therapy (HAART) and achieve HIV viral load copies below 50 copies/mL.[34,35] There are a number of other assays e.g. for Hepatitis B virus which is important for monitoring disease progression and for assessing the response to antiviral therapy[36] and also quantitative

Hepatitis B virus PCR is been used as a guide employers e.g. healthcare workers who are infected with Hepatitis B virus in the UK and whose viral load rose above 103 genome-equivalents/ml should are restricted from performing exposure prone procedures for as long as their viral load remained above that level.[37]

***Parasites, Fungi, and Protozoa***

Over the past 20 years, dramatic advancements have occurred in the molecular approach to the investigation of parasites and parasitic diseases. RT-PCR methodology has been efficiently used to detect, differentiate, and diagnose parasites that infect humans and animals. Among parasitic infections, RT-PCR has been applied most vigorously in the diagnosis and detection of drug resistance genes of *Plasmodium spp* - causative agents of malaria. Specific RT-PCRs have been developed to diagnose *Toxoplasma gondii*, *Trypanosoma cruzi*, *Babesia spp.*, *Leishmania spp.*, *Cryptosporidium parvum*, Entamoeba, and *Giardia spp*. The traditional culture method, animal inoculation, and serological detection are not only time consuming but also lack of sensitivities. RT-PCR vastly improved speed and sensitivity of diagnosis of such parasites with impact on clinical management and epidemiological investigations.[38-45]

RT-PCR assays can also be successfully applied to the diagnosis of diseases caused by *Aspergillus fumigatus* and *A. flavus*. The rationale behind this effort is that timely detection of *Aspergillus spp.* may decrease the extreme morbidity and mortality associated with invasive aspergillosis by initiating antifungal therapy in a timely manner, particularly in immunocompromised individuals. RT-PCR can also detect A. fumigatus mutations that confer high-level resistance to antifungals.

The use of RT-PCR has also been of great use in identification of Cryptococcal disease which has become a major fungal infection in patients infected with HIV and AIDS patients. In addition PCR has been used in the early identification of *Pneumocystis jirovecii* the causative organism on Pneumocystis pneumonia (PCP).

High sensitivity of this method makes the assay appealing in the identification of this organism in immunocompromised patients which can help clinicians confirming their clinical suspicion on the basis of risk factors, Chest-XRay findings and pulse oximetry which ultimately leads to early initiation of appropriate treatment that in turn can improve outcome and shorten the patient's hospital stay.[46-48]

## Conclusion.

Numerous technological advances have been made using PCR since its discovery in the mid-1980's. RT-PCR is one of the enabling technologies of the genomic era and has become the method of choice or the gold standard for the detection of nucleic acid. Prior to the development RT-PCR, quantitative PCR was very labor intensive. Real-time technology has significantly extended the use and scope of RT-PCR assays, with the potential for quantification of nucleic acid targets a particular advantage. RT-PCR offers streamlined assay development, reproducible results, and a large dynamic range. The focus on nucleic acid quantification, together with the introduction of advanced uncomplicated instrumentation and chemistries, has facilitated the migration of this technology from research laboratories into individual diagnostic laboratories. Despite some of the difficulties that may still need to be worked out, the foundation has been set for the use of quantitative RT-PCR in routine diagnostic laboratories. This is reflected in the increasingly significant role it plays in clinical diagnosis in infection and infectious diseases, in particular when used to determine the viral load and disease progression. The technology can generate large amounts of data within a relatively short time. The accuracy of the obtained data is largely depended on several factors including; the choice of chemistries, primers and probes, and instruments. Appropriate application, quality control and standardization are also important matters and must be considered, it is vital to take time to evaluate each stage of the development protocol, starting with laboratory setup, sample acquisition and template preparation, and the RT-PCR steps. Only if all of these stages are appropriately validated is it possible that molecular diagnosticians can reliably interpret data to clinical colleagues to have the best positive impact on patients' outcome.

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**Acknowledgements**
*We would like to thank Editorial Staff of the International Journal of Medical Students, for giving us this opportunity to write this review.*

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

**Cite as:**
*Saeed KBA, Ahmad SN. Real-Time Polymerase Chain Reaction: Applications in Diagnostic Microbiology. Int J Med Students 2013;1(1):28-36.*

# Cerebellar Syndromes: A Medical Student Guide

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## Abstract.

The cerebellum is central to normal motor function and co-ordination, and can be frequently affected in a number of common disease processes. However, medical student teaching relating to cerebellar anatomy and pathology is lacking, leaving many graduates with a significant knowledge gap. Junior doctors need to be able to recognize 'cerebellar syndromes' on presentation to hospitals, and to identify and manage reversible causes rapidly and effectively. After review of relevant literature, a simple approach to the functional anatomy and practical classifications of common cerebellar pathology is presented here, with a focus on symptoms, signs and examination techniques essential to medical school final exams.

**Keywords:** Cerebellar Diseases; Central Nervous System Diseases; Cerebellum; Students, Medical (Source: MeSH, NLM).

## Introduction.

The cerebellum (Latin for 'little brain') is located infero-posteriorly to the cerebral cortex, and is fundamental to normal neurological functioning, yet it was not until the early 20th Century that Flourens discovered its primary function to be in motor control and co-ordination.[1] The cerebellum may be affected in common neurological disorders such as stroke, multiple sclerosis and mass lesions, often producing a 'cerebellar syndrome'. Junior doctors need to be confident in recognition and investigation of patients presenting with cerebellar symptoms and signs appropriately in order to identify treatable causes and provide accurate prognosis. Textbook coverage of this area is notoriously disjointed, often leaving medical students with a significant knowledge gap. This article aims to provide a brief overview of the etiology of cerebellar disorders and a simple approach to history, examination and investigation of patients presenting with cerebellar syndromes.

## Methodology.

A review of literature was performed using PubMed, Google Scholar, Embase and Medline databases for articles from 1975 to 2012 using the search terms: Cerebellum, Neurological Examination, Ataxia, and Cerebellar Syndromes. Additional papers were retrieved from reviews and references. Articles included were in the English language and related to anatomy and clinical examination technique of the cerebellar system.

## Anatomy.

The cerebellum is attached to the dorsal aspect of the brainstem by three separate fibrous structures - the superior, middle and inferior peduncles, which connect to the midbrain, pons and medulla respectively (Figure 1). It comprises two hemispheres joined in the midline by the 'vermis', which, unlike the cerebral hemispheres, are ipsilateral in their control of co-ordination. Afferent input to the cerebellum includes neuronal tracts from the semicircular canals, proprioception via the spinal cord, motor information from the frontal lobes, and fibers from reticular nuclei in the brainstem. Efferent output is to midbrain and thalamic nuclei, or directly to the motor cortex, permitting feedback comparing sensory and motor input with output.

The anatomy of the cerebellum can also be further divided functionally. Control of balance, posture and eye movements is mediated by the flocculonodular lobe (or archicerebellum) which connects with the vestibular and reticular nuclei in the brainstem. The vermis and paravermis (the intermediate section between the cerebellar hemispheres) together make up the paleocerebellum, responsible for control of postural and distal muscle tone. Finally, coordination and planning of limb movement occurs within the neocerebellum, which is comprised of the remaining cerebellar hemispheres.[2]

### *Etiology of Cerebellar Disease*

Cerebellar pathology arises secondary to a broad range of etiologies which can be usefully classified according to the time-course of symptoms:

*1. Acute onset (seconds to minutes)*

Usually cerebellar infarction or hemorrhage. This may be

*Abbreviations Index:*
**CJD, Creutzfeld-Jacob Disease**
**CSF, Cerebrospinal Fluid**
**CT, Computed Tomography**
**CXR, Chest X-ray**
**GI, Gastrointestinal**
**HIV, Human Immunodeficiency Virus**
**MRI, Magnetic Resonance Imaging**
**OSCE, Objective Structured Clinical Examination**
**TIA, Transient Ischemic Attack**

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*Submission: 2012, Jan 4.*
*Accepted: 2012, July 10.*
*Process: Peer-Reviewed.*

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associated with headache, vertigo, vomiting and altered consciousness.

*2. Sub-acute ataxias (hours to days)*

- Inflammatory causes – most commonly multiple sclerosis
- Viral – (more common in children) associated with pyrexia, dysarthria, limb & gait ataxia.
- Paraneoplastic cerebellar degeneration. Particularly carcinomas of ovaries and lung.
- Other - hydrocephalus, posterior fossa tumors, abscesses, parasitic infections, toxins.
- Alcohol excess

*3. Episodic ataxias*

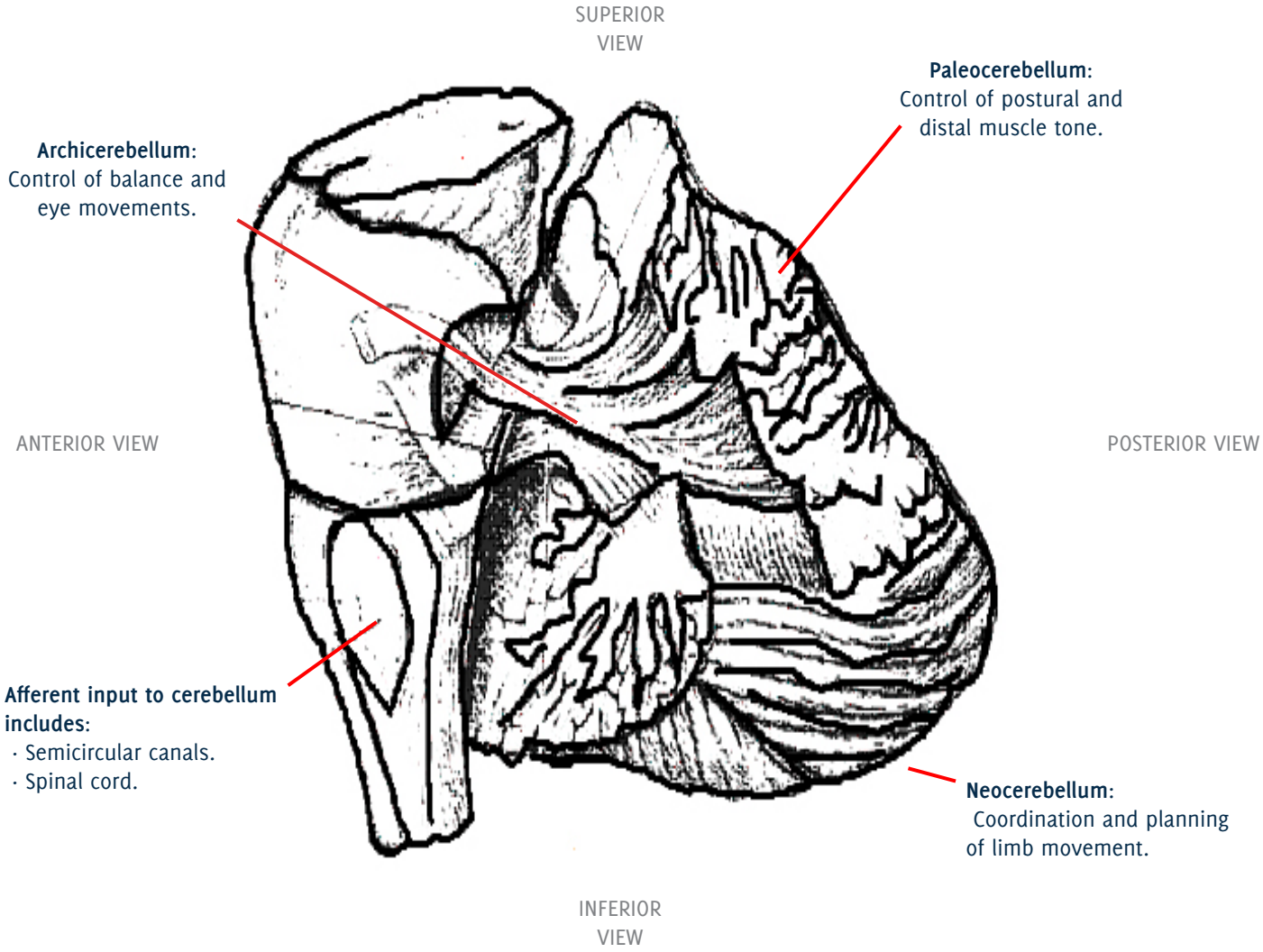
Usually transient and last minutes to hours, there are various causes:

- Drugs: Barbiturates, Phenytoin and other Anticonvulsants, Anti-neoplastic drugs
- Transient posterior cerebral circulation (vertebrobasilar) ischemic attacks
- Foramen magnum compression
- Inherited episodic ataxias

*4. Chronic progressive ataxias (months to years)*

- Chronic alcohol excess
- Malnutrition (including thiamine, zinc and vitamin E deficiencies).
- Drugs - particularly anticonvulsants such as phenytoin (may reverse once withdrawn)
- Structural lesions (slowly progressive tumors or vascular malformations)
- Inherited: Including Friedreich's ataxia, spinocerebellar ataxias
- Degenerative: Including multiple system atrophy, idiopathic late onset ataxias
- Rarer causes: Chronic solvent abuse, heavy metal exposure, prion diseases (including sporadic CJD)

***Figure 1.*** *Anatomy of the Cerebellum.*



A 'surgical sieve' approach to the commoner causes is illustrated in Table 1.

***Symptoms and signs of cerebellar disease***

The cerebellum operates at a subconscious level to control muscle tone, posture and co-ordination. Cerebellar disorders result in difficulties with the rate, rhythm and force of limb movements, gait and speech.[3] The key symptoms and signs can be remembered using the mnemonic DANISH:

- ***D***ysdiadochokinesis – Inability to perform rapid alternating movements, especially of limbs.
- ***A***taxia – Inco-ordination of voluntary movements. This includes 'dysmetria': inability to accurately judge distance, leading to over- or under-shooting of targets and unsteady gait.
- ***N***ystagmus – Rapid, involuntary movement of the eyes.
- ***I***ntention tremor - Tremor exacerbated by voluntary goal-directed movements.
- ***S***canning dysarthria - Jerky, sometimes explosive, slurred speech, with difficulties maintaining rate, rhythm and force resulting in separated syllables.
- ***H***eel-shin ataxia.

Patients may also present with symptoms relating to underlying pathology for example, headache, nausea and vomiting resulting from a cerebellar tumor; systemic upset associated with a cerebellar abscess, and pyramidal and sensory signs in multiple sclerosis.

***Figure 2.*** *CT head scan showing right sided cerebellar hemorrhage. This elderly patient presented with sudden onset headache, nausea, vomiting, unsteady gait and right sided clumsiness.*

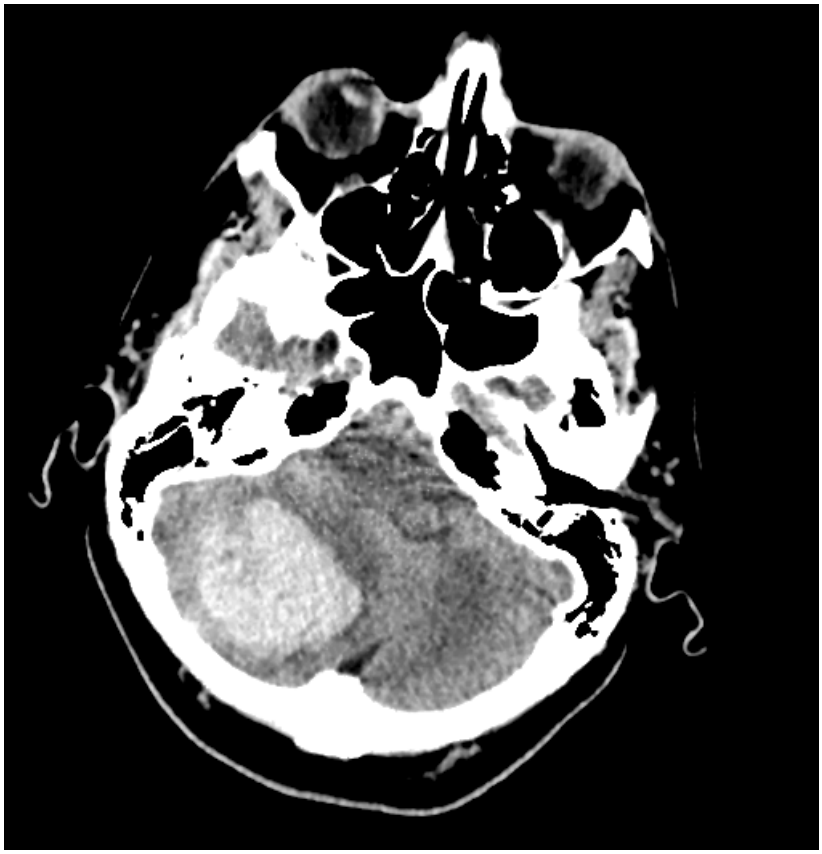
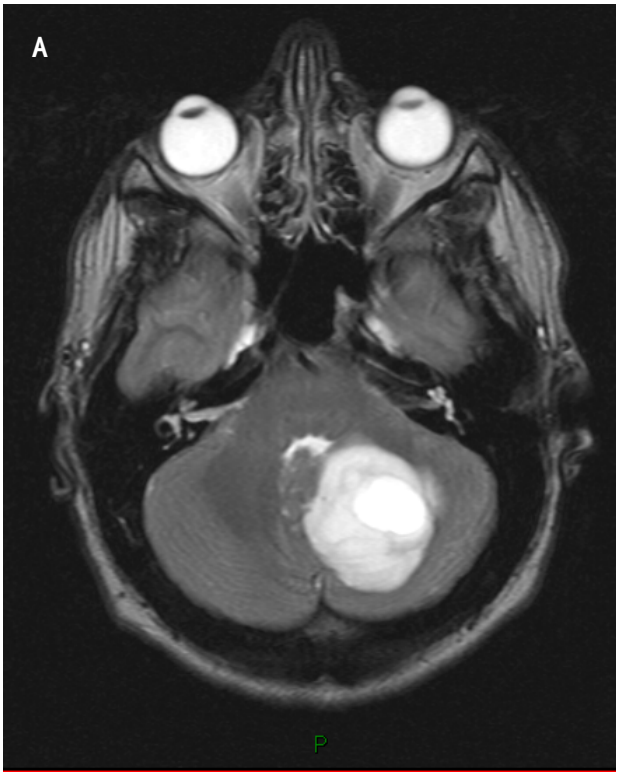
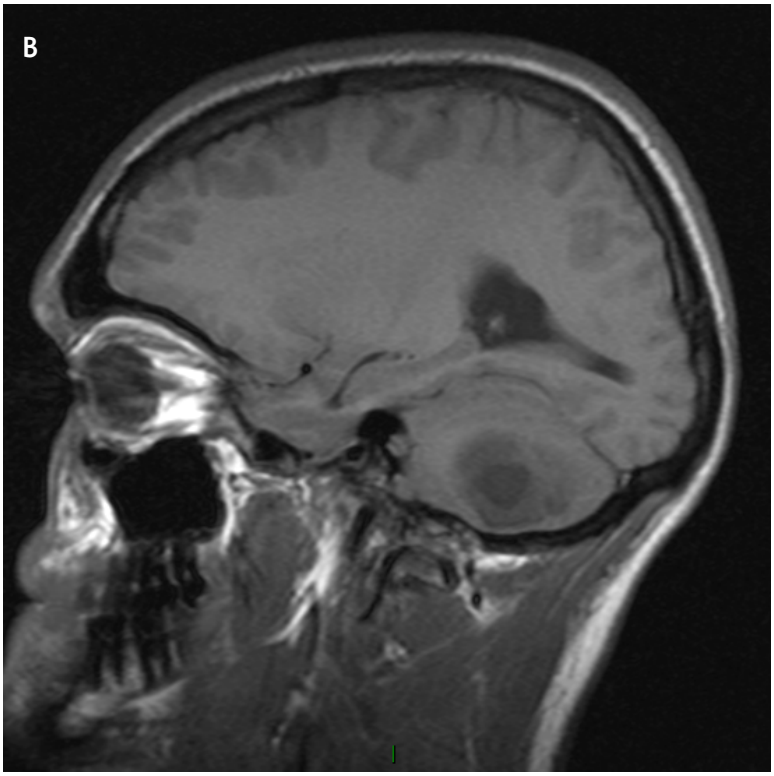


***Figure 3.*** *A (axial section) and B (sagittal section). MRI head scan showing mixed solid/cystic left cerebellar hemisphere mass with hydrocephalus and cerebellar tonsillar herniation caused by a pylocytic astrocytoma. This young patient presented with a subacute left sided cerebellar syndrome associated with headache.*



A guide to comprehensive examination of cerebellar function as may be expected in an undergraduate Objective Structured Clinical Examination (OSCE) is presented in Table 2.

Handy Hints:

1. Romberg's sign is often mistakenly attributed to cerebellar dysfunction. It is actually primarily a sign of pathology affecting the dorsal columns.[4] The patient stands with their feet together and eyes closed; if they lose balance, the test is positive. Postural hypotension, anxiety and axial stiffness are potential causes of a false positive Romberg's. In cerebellar ataxia, the test is not positive: the patient cannot balance with eyes open
2. Note that rapid repetitive movements can also be used to detect non-cerebellar problems; for example, in upper motor neuron lesions these movements are slow and deliberate, and in extrapyramidal conditions such as Parkinson's the movements start slowly, and may be small in amplitude and slow in speed.
3. In disorders which predominantly affect midline cerebellar structures (tumors of the vermis/alcohol-induced damage), the finger-nose test, heel-shin test and testing for dysdiadochokinesis may be normal. It is therefore of important to check the stance and gait in cerebellar examination, as truncal ataxia may be the only abnormal finding.

***"Overall, specific tests can be helpful in confirming or refuting the presence of cerebellar disease, but must be interpreted in the context of other signs and the case history."***

***Investigation of Cerebellar Disease***

Investigation should be guided according to the differential diagnoses in mind, but commonly includes blood tests and cerebellar imaging.

***An approach to investigating cerebellar disorders:***

- Toxic: Review drug charts, interactions, toxicology screen.
- Infectious: Temperature, pulse and blood pressure, full blood count, blood cultures.
- Metabolic/endocrine: Thyroid function, caeruloplasmin, copper, thiamine, blood glucose.
- Inflammatory (including multiple sclerosis): CSF examination for white cell count, protein and oligoclonal bands.
- Neoplastic/Paraneoplastic: CXR, body imaging, tumor markers, paraneoplastic antibodies.
- Genetic: Blood testing for genetic mutations – Friedrich's ataxia, spinocerebellar ataxias.

Imaging: Computed tomography (CT) (Figure 2) or Magnetic resonance tomography (MRI) (Figure 3) of the brain are used to investigate cerebellar disorders and may reveal a stroke, space occupying lesion, demyelination or atrophy.

## In Summary.

The cerebellum is affected by a number of common disease processes, producing characteristic symptoms and signs. Junior doctors need to be able to accurately detect such 'cerebellar syndromes' since they are a common presentation to hospital and since there are a number of treatable causes which can be reversed if detected early.[5] A sound understanding of the anatomy of the cerebellum, etiology of cerebellar disorders and logical approach to examination will facilitate appropriate investigation and treatment.[6]

- Causes of cerebellar disease: Commonly stroke/TIA; multiple sclerosis; mass lesions including primary tumors, metastases and abscesses; drugs; alcohol and metabolic abnormalities.
- Symptoms of cerebellar disease: Difficulties with coordination, intention tremor, gait disturbance, slurred speech.

***Table 1.*** *'Surgical Sieve' approach to common causes of cerebellar syndromes. * Denotes common cause.*

| | |
|---|---|
| Vascular | Stroke (infarct or hemorrhage)*, Transient ischemic attack* |
| Inflammatory | Multiple sclerosis* |
| Neoplastic | Primary tumors: Astrocytoma, Medulloblastoma, Haemangioblastoma |
| | Secondary tumors: metastases* (commonly lung, breast and GI tract) |
| | Paraneoplastic phenomena (Anti Hu Ab in small cell lung cancer) (rare) |
| Toxic/Trauma | Alcohol* |
| Metabolic | Hypoglycemia*, Hypoxia*, Hypothyroidism*, thiamine deficiency* |
| Infectious | Bacterial: Meningo-encephalitis, Intracranial abscess, Viral: Varicella, HIV |
| | Parasitic infections(rare): Toxoplasma, Falciparum Malaria |
| Congenital | Agenesis, Dandy-Walker malformation, Arnold-Chiari malformation (rare) |
| Inherited | Friedrich's Ataxia, spinocerebellar ataxias |
| Degenerative | Multisystem atrophy, Spinocerebellar ataxias, prion disease (rare) |
| Drugs | Barbiturates*, Phenytoin and other Anticonvulsants*, Anti-neoplastic drugs*. |

*Table 2. A systematic approach to cerebellar examination. 'Please examine this patient's cerebellar function'. How to pass the OSCE.*

| | Action | Potential Findings |
|---|---|---|
| Introduction | Wash your hands.<br>Introduce, explain, consent the patient.<br>Position the patient at 45° lying down. | |
| Inspection | Bruising, scars<br>'bobbing ' head<br>Walking aids | Recurrent falls<br>Titubation<br>gait ataxia |
| **Head** | | |
| Nystagmus | Follow your finger with eyes, head still | Broken pursuit, nystagmus the degree of involuntary eye movement is greatest when gaze is focused to the same side as the lesion. |
| Speech | Ask to repeat 'West Register Street, British Constitution, PP PP PP, KK KK KK, TT TT TT'<br>Ask to read a sentence aloud | Staccato Speech<br>Slurring |
| **Limbs** | | |
| Tone | As in normal neurological exam | May be increased after a stroke or in multiple sclerosis. |
| Power | As in normal neurological exam | May be reduced with associated upper motor neuron pathology. ↓ power may confound incoordination |
| Coordination | UPPER LIMBS<br>Test for 'rebound':<br>-Arms out straight in front with eyes closed, push each arm down ~ 10cm then release6<br><br>Finger-nose Test<br>Examiner holds index finger about 50cm in front of the patient's face, and asks the patient to go between touching his/her nose and the examiner's finger as accurately as possible.<br><br>Hand-turning test<br>Ask the patient to tap one hand on the back of the other, and then tap the same spot with the dorsum of the same hand. | Overshooting = Dysmetria<br><br>Difficulty = Dysmetria<br>Intention tremor, past pointing<br><br>Difficulty = Dysdiadochokinesis |
| Coordination | LOWER LIMBS<br>Heel-shin test<br>Put heel onto opposite knee and slide heel down shin to ankle. Lift off and repeat.<br>Foot tapping<br>Ask to tap foot as rapidly as possible | Intention tremor<br>Difficulty = Dysmetria<br><br>Difficulty = Dysdiadochokinesis |
| **Posture and Gait** | | |
| Posture | Ask how stable they are sitting/standing?<br>Assess sitting down<br>Also with arms crossed<br>Assess standing (If stable sitting)<br>Arms by sides, feet together | Truncal ataxia<br><br>Truncal ataxia |
| Gait | Ask to walk across room<br><br>Ask to walk heel to toe | Wide-based gait (midline cerebellar lesions)<br>Unsteadiness and lateral veering (hemispheric lesions)<br>Irregular steps |
| **Concluding Remarks** | "I would also like to carry out a full neurological examination"<br>Investigations: MRI posterior fossa, and specific as indicated (see text) | |

- Signs of cerebellar disease: **D**ysdiadochokinesis & Dysmetria, **A**taxic gait, **N**ystagmus, **I**ntention tremor, **S**canning dysarthria, **H**eel-shin test ataxia (remember DANISH).

Investigations: Blood tests, Imaging, CSF examination and genetic screening as appropriate.

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

**Cite as:**
*Sellers CK, Pal S. Cerebellar Syndromes: A Medical Student Guide. Int J Med Students 2013;1(1):37-42.*

# A Case of Sarcoidosis Disseminated to Skeletal Tissues

Edon Rabinowitz[1], Chinwe Ogedegbe[2], Joseph Feldman[2].

## Abstract.

Sarcoidosis is a systemic granulomatous disease of unknown etiology that typically affects young adults. Diagnostic criteria for sarcoidosis include involvement of two or more of the following organ systems: 1) pulmonary infiltrates; 2) bilateral hilar adenopathy; and 3) skin and/or eye lesions. Musculoskeletal system is less commonly involved. For that reason potential presenting symptoms can vary and make the diagnosis very challenging; particularly if a patient has symptoms that mimic other conditions. Musculoskeletal involvement for example can mimic malignancy. The following case describes a patient with known history of primary metastatic mediastinal Germ Cell Tumor (GCT) with teratomatous elements who is diagnosed with sarcoidosis involving skeletal tissues.

**Keywords:** Sarcoidosis; Musculoskeletal System; Neoplasms, Germ Cell and Embryonal (Source: MeSH, NLM).

## Introduction.

Sarcoidosis is a chronic inflammatory disease, characterized by noncaseating granulomas, which can affect any organ, but most commonly the lungs. The diagnosis of sarcoidosis is one of exclusion after ruling out pathologies such as mycobacterial, fungal infections, malignancy etc. The etiology of Sarcoidosis is unknown but is theorized to be an infectious or noninfectious environmental agent that triggers an inflammatory response in a genetically susceptible host. Clinical features include nonproductive cough and shortness of breath on exertion. Hallmark findings include bilateral hilar adenopathy on chest x-ray and elevated serum Angiotensin-converting enzyme and calcium. Systemic findings include erythema nodosum, uveitis, arthralgias and arthritis. Sarcoidosis is typically managed with systemic corticosteroids.[1]

Cases of Sarcoidosis are annually documented worldwide at varying incidence rates. Diagnosis most often occurs under the age of 50-years-old, peaking in the 3rd and 4th decades of life[2] with the highest incidence (5-40 cases per 100,000) reported in Northern European nations, particularly Ireland and Scandinavia.[3] In the United Sates, African Americans are approximately three times more likely to be affected by sarcoidosis compared to Caucasians (35.5 cases per 100,000 versus to 10.9 cases per 100,000 respectively).[4] Despite geographic and racial differences, sarcoidosis uniformly shows a greater preponderance towards females. [5]

It is well documented that over 90% of cases of Sarcoidosis have pulmonary, cutaneous or ocular involvement with little of no skeletal involvement.[6] Even though detection of osseous involvement in Sarcoidosis has been increasing due to improved imaging techniques such as MRI and PET, true incidence rate have been difficult to assess for several reasons. First is the asymptomatic nature of osseous involvement. Secondly, because when symptoms of bone pain do exist, their diagnosis is obscured by classic musculoskeletal clinical manifestations of Sarcoidosis including arthralgias, sarcoid arthritis and sarcoid myopathies. Thirdly, as seen in the case to be described below, because skeletal involvement in Sarcoidosis can be misinterpreted as metastatic involvement of the bones. Radiographically reported incidence of skeletal involvement in the setting of Sarcoidosis occurs in only 5% of patients. [7]

## The Case.

A 33-year-old Caucasian male, with past medical history significant for mediastinal Germ Cell Tumor (GCT), presented to the emergency department (ED) with 2-month history of worsening exertional dyspnea. When diagnosed with GCT 3 years ago, CAT scan imaging of his chest showed pathologically enlarged lymph nodes extending from the anterior mediastinum into the middle mediastinum measuring 8.1 x 10.0 cm on the right and 8.0 x 9.6 cm on the left. Subsequent lymph node biopsy revealed immature GCT consisting predominantly of yolk sac tumor with teratomatous component. Testicular ultrasound was unremarkable at that time.

The patient's dyspnea significantly worsened over the week prior. He reported a productive cough with clear sputum and denied palpitations or chest pain. On physical exam

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*Submission: 2011, Dec 6.*
*Accepted: 2012, March 26.*
*Process: Peer-Reviewed.*

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he was afebrile, tachycardic, and tachypneic and found to be in moderate respiratory distress. Bibasilar crepitus was noted and arterial blood gas revealed a Pa02 of 57.3 mmHg on room air, indicating hypoxemia. A follow up CAT scan revealed a 14.4 x 11.3 cm anterior mediastinal mass with diffuse reticulonodular infiltrates in both lungs. Subsequent left lung video-assisted thoracoscopy and biopsy found predominantly well-defined large multinucleated giant cell granulomas consistent with Sarcoidosis. The patient was started on oral steroid therapy without improvement in his symptoms.

***Figure 1.*** *Abnormal hypermetabolism of the left trochanteric region. These PET/CT images were interpreted by evaluation of both the anatomic (CT) and metabolic (PET) data which were electronically fused.*

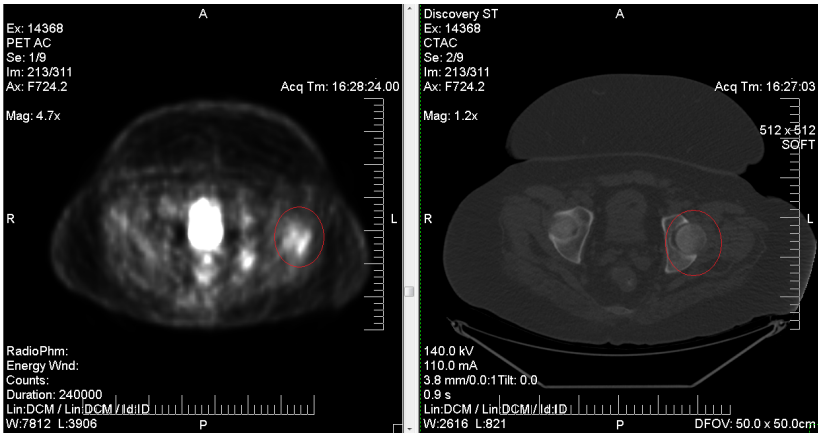



***Figure 2.*** *Abnormal hypermetabolism corresponding to L3 vertebra.*

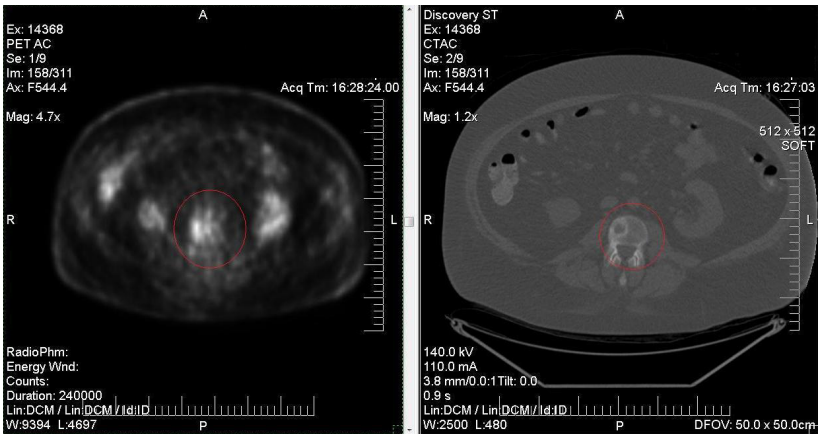
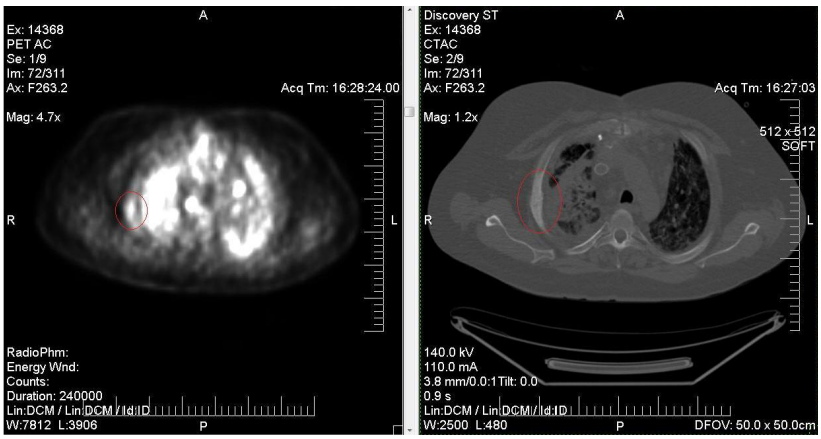



***Figure 3.*** *Mild abnormal hypermetabolism in fusiform fashion of the right third lateral rib. Additional non-osseous regions of hypermetabolism are seen corresponding to pathologically enlarged mediastinal and hilar lymph nodes. .*




Over the ensuing 6 months the disease progressed and he presented to the ED once again with superior vena cava syndrome. Soon after, due to compression, the patient developed a pericardial effusion with signs of heart failure and underwent mediastinal debulking. Surgical pathology revealed a 12.5cm mature teratoma with extensive necrosis. He reported chronic fatigue, exertional dyspnea, and a racing heart without fever or chest pain and was placed on home oxygen and BiPAP due to chronic hypoxemia. A PET/CT was performed to evaluate suspicions of GCT dissemination. Results showed abnormal hypermetabolic foci in the mediastinal lymph nodes, left hilum and subcarinal lymph nodes, periportal, peripancreatic and aortocaval lymph nodes. Hypermetabolic foci were also noted in multiple osseous lesions including the proximal femoral shaft, left trochanteric region, lumbar vertebra, and right third lateral rib. Subsequent left iliac bone core biopsy and FNA revealed bone marrow with numerous epithelioid granulomas in a background of normocellular bone marrow consistent with sarcoidosis. The patient never complained of bone pain.

## Discussion.

The described patient was found to have multiple painless bone lesions on imaging studies related to his GCT. Given the extensive and well-documented history of GCT, the leading diagnosis after the PET/CT revealed the skeletal lesions was first thought to be metastatic disease. However it is important to keep in mind that at the time the patient already had an established diagnosis of Sarcoidosis. Other differential diagnosis for multiple skeletal lesions can include multiple myeloma, brown tumors of hyperparathyroidism, lymphoma, histiocytosis, osteomyelitis, Paget's disease, and fibrous dysplasia.

The incidence of Sarcoidosis with skeletal involvement has been speculated to range from 3% to 38%.[5-7] However, skeletal Sarcoidosis may or may not cause significant musculoskeletal manifestations. Therefore, since most patients are asymptomatic and radiologic examination is not routinely performed, sarcoid bone lesions could go undetected and true incidence of skeletal Sarcoidosis could be underestimated. If it was not for our patient's GCT, he likely would not have required imaging studies.

Skeletal involvement has been documented more frequently in the phalanges as compared to the long bones, vertebra, skull and pelvic bones.[11] Our patient had no involvement of the bones of his hands or feet but rather involved his long bones, pelvic bones, vertebra and ribs. Pure skeletal involvement is rare in the setting of Sarcoidosis. The presence of skeletal sarcoidosis does not seem to have an impact

on the degree of respiratory dysfunction.[8] However, it is difficult to assess to what degree Sarcoidosis contributed to his pulmonary symptoms as he had an extensive primary tumor located in his mediastinum.

Since our patient was being followed and treated for his GCT, we had the luxury of knowing that previous imaging studies did not show any skeletal involvement. It is quite certain that pulmonary sarcoidosis involvement preceded the skeletal involvement in this case. As stated above, since radiologic studies would not routinely be preformed, normally it would be extremely hard to determine whether skeletal sarcoidosis preceded pulmonary and mediastinal involvement or if sarcoidosis first presented with pulmonary and mediastinal manifestations.

Regarding laboratory testing, elevated inflammatory markers and ACE levels are more frequently found in sarcoidosis with skeletal involvement.[9] However our patient had both pulmonary and skeletal involvement as well as a cancer, which could all contribute and affect inflammatory markers and alter lab data.

First line therapy for sarcoidosis has traditionally been systemic corticosteroids while refractory cases have often been managed with Methotrexate.[10] The combination of history of GCT with prior surgery and chemotherapy, along with a wide spread dissemination of sarcoidosis in our patient, creates a challenge to the more traditional sarcoidosis treatment methods particularly because there is increased likelihood of infection due to impaired immunity.

In this case, the imaging features that were unexpectedly found to be sarcoid rather than metastasis would likely be considered as nonspecific and yield a broad differential diagnosis in many scenarios. Previous data suggests that, although rare, osseous involvement in sarcoidosis can be differentiated from a destructive lytic bone lesion by the absence of periostitis on conventional radiography.[15] However, definitive diagnosis can only be made with biopsy, which is necessary to rule out metastatic disease. In the future, appropriate use of PET scan may help in timely detection of osseous involvement in patients with sarcoidosis.[16]

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**Acknowledgements**

*I would like to acknowledge Hipen Shah, a 4th Year Biology Major at New Jersey Institute of Technology and aspiring physician, for his help in completing the final steps of this project.*

**Conflict of Interest Statement & Funding**

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

**Cite as:**

*Rabinowitz E, Ogedegbe C, Feldman J. A Case of Sarcoidosis Disseminated to Skeletal Tissues. Int J Med Students 2013;1(1):43-5.*

IJMS International Journal of Medical Students



# Research: A Pathway Towards a Good *Curriculum Vitae*

Muhammad T. Shakoor[1], Samia Ayub[2], Zunaira Ayubs[3].

## The Experience.

Nowadays there is a lashing trend of doing fellowships. Residency and fellowship positions have become very competitive. From my experience, I found that the majority of candidates who aspire to apply for residency or fellowship positions don't have any significant research backgrounds. Being a medical student myself, I should not blame any other student for this deficiency, as most of the medical schools don't provide basic atmosphere, guidance and infrastructure for undergraduate research activities. By the time students graduate and apply for a residency spot or fellowship position after residency, they have no research credentials with them other than their degree requirements and a few certificates for extracurricular activities. One should realize that these accomplishments merely provide a skeleton for your *Curriculum vitae* (CV) in order to add depth to your CV you have to be able to include research experiences (that you have acquired during your undergraduate degree), as well as good recommendation letters and advanced clinical experience.[1] Research work in your CV will help set you apart. When you go for a job interview, having a strong research background and independent work gives you something to talk about that the interviewer will be interested in. As a student, any efforts in the field of research are highly appreciated. Above all, research training will make you a better-equipped physician with a sharper mind and stronger critical thinking skills.

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When you put your research work on your CV, it should be something appealing. If you tell them that you have done some statistical analysis work, some repetition of the published work or some substandard work as part of your community medicine posting, there are high chances that your CV may not appeal to the interviewer.

Most medical students think that research is for postgraduate students and research fellows only. Please, don't think you aren't smart enough to get involved. What you may lack is experience, but not intelligence. I have no doubts that every medical student is qualified enough to do independent research. Moreover, you can attain admission to a MS (Master of Science) program to develop research experience and participate in publications, though this may be an over expensive business. The total expenditure for a semester for MS in US can vary from $6,500 to $20,000.[2] However, a good MS degree from a reputed university in UK can get you around £5,400 to £7200 per annum.[3]

Now the question is how to get started? I have few answers and suggestions to it and hope that it might help the beginners if not everyone. For the convenience of students I have put all this in answer question pattern.

***Q. Will it affect my studies?***

A large part of medical student community thinks that it can affect our studies but ideally speaking, not much. You are all smart enough to maintain a balance between the two. Especially, at first you'll probably find out that doing research is not so easy; expect it to be challenging. You will find out very early on where your true strengths and weaknesses lie. You are going to find out how motivated you are to be successful. If you remain committed, you are going to learn to solve your own problems and you are really going to find out what it means to be a lifelong learner.

***Q. Should I start with Independent studies?***

Without a doubt, I would like to see every student electing to do an independent research study. I strongly encourage every student who has not yet done so to make a genuine and full commitment to work with at least one of your graduate school faculty members. I recommend you do your initial work with a "CAPE" mentor (Capable, Available, Project interests you, Easy to get along with) because you will get plenty of support from him.[4] You may need it, especially when you start out, but with time you will learn how satisfying it is to be independent.

***Q. How do I find a mentor?***

The answer is, when you have narrowed your interests down to one or more broad areas (specialties), you can seek advice when choosing a mentor, and also ask for suggestions on which labs would be good for short-term students. Talk to the faculty. Don't be shy; every faculty

*Submission: 2012, Feb 10.*
*Accepted: 2012, March 26.*
*Process: Peer-Reviewed.*

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member would love to talk with you about his or her own research interests. You might start with your course directors and lecturers, if their expertise is in one of your areas of interest. You can also e-mail or make appointments with the relevant Department Chairs or Division Chiefs, Directors of Centers or Institutes, and Graduate Group Chairs or track chairs. Some of these folks will be extremely busy, and you may have to be persistent. Don't give up after one e-mail if you don't hear from someone. You should also get the advice of your fellow students, senior students who have already been through this process. Once you have a list of particular labs that you are interested in, contact those faculty members directly, perhaps by e-mail. Tell them about your enthusiasm for their research and ask if they would be interested in having a medical student in the lab. If so request a chance to meet with them to discuss possible projects. If not, perhaps ask if there are others they would recommend.

***Q. Should I do research in a competitive field?***

The answer here is to do substantive research that you are interested. The key is to find something you are passionate about. Find out what is going on in your major area or even in areas outside of your majors. Talk to the other students who are or have done independent study projects. Identify a topic that seems interesting to you. Don't think you have to immediately come up with your own original ideas for a project. There are plenty of good project ideas that you can develop as you gain experience. If you do have your own idea, that is great too.

***Q. What are the research opportunities available for undergraduates?***

Another factor that bothers some of the students is Research Opportunities at Undergraduate level. By the way, there are various opportunities; the only thing you should know is how to tap them. For example, there are a lot of institutions that sponsor Medical Student Summer Fellowship Program, an eight-week research program offered to medical students.[5] This is just one example but these opportunities may vary from country to country and institution to institution. No one can find them for you; it is you who has to find them. You can ask other students who are doing research work or you can ask the faculty members.

***Q. How could Medical Schools help their students?***

Well I have a suggestion here; "Research Cells" should be integral part of every Medical Institution to promote research methodology awareness in medical students by frequent arrangements of research workshops, seminars and arranging research competitions. Because this is always the first step that looks impossible, so institutions are supposed to help their students in their first step. There should be a requirement in curriculum that should obligate students to do independent study or research. Students should be included as co-authors. Monetary compensation for work must also be rendered, as it would be if the assistant was a non-student. Every medical school should open paid research spots especially in summer vacations that will work as an incentive.

For those who have not yet initiated independent research projects, please seriously consider doing so. If you have already done independent research and have found it to be one of your best college experiences, congratulations to you! If you did an independent project, and it was not fully satisfying, try again, perhaps with another mentor.

More importantly, I really do hope that you will discover for yourselves what I have discovered for myself that doing independent research was absolutely the very best educational experience of my entire college career. Please, get started as soon as you can.

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**Conflict of Interest Statement & Funding**

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

**Cite as:**

*Shakoor MT, Ayub S, Ayubs Z. Research: A Pathway Towards a Good Curriculum Vitae. Int J Med Students 2013;1(1):46-7.*

IJMS International Journal of Medical Students



# A Reflection and Comparison of Physician Training in the United States of America and United Kingdom

Rohit S. Aiyer[1].

## The Experience.

As a final year medical student at the University of Birmingham in England, I am very familiar with the training structure of physicians in the National Health Service (NHS). Recently, I had the opportunity to do 4 months of clinical electives at the University of Massachusetts in Worcester, Massachusetts and Mount Sinai Medical Center in New York City, New York. This experience allowed me to gain insight on the American training system for medical student graduates that provided a new perspective on physician training. The following reflection will be based on my experiences in the two countries and focus on the working guidelines for junior doctors in the United States that is based on the Accredited Council of Graduate Medical Education (ACGME) Duty Hours protocol, and will be compared to the European Work Time Directive (EWTD) guidelines for British junior doctors.

### *Structure of Training Systems in the U.S and UK*

In the following text, Foundation year doctors are physicians in the UK who have just graduated from medical school, whereas registrars are more senior junior doctors who are pursuing specialized training in a particular field to become a consultant. Interns in the U.S are similar to foundation year doctors, as they are also physicians that have just graduated from medical school, and residents are more senior junior doctors who are specializing in a field. In the UK the training system entails of being a foundation year doctor for 2 years, and then another 6-8 years as a registrar depending on the specialty, before becoming a consultant. In the U.S, recent medical student graduates are interns for 1 year, and then are residents for 3-4 years, again depending on the specialty. After completing residency, the physician can choose to stay as a consultant or further specialize for 1-3 years by doing a fellowship in a sub-specialty.

### *Residency Training in America*

After investigating the training system in the U.S, it should be noted that the ACGME in 2011 introduced a new set of guidelines for the work hours of residents. Previously the working hours were based on the 2003 ACGME guidelines, which stated that residents had a limit of working 24 hours in one shift, with a maximum of 6 additional hours of education learning. Consequently, they could not work more than 30 hours continuous at one time. This has now been changed to 16 hours as of July 1, 2011, and interns by law are supposed to have a minimum 8 hours of rest between any 2 shifts. Residents have to work 24-hour shifts with an additional four hours of work education learning purposes, or a total of 28 hours continuous.[1]

Based on my interaction with residents of different specialties it became apparent that the new changes to the working guidelines were positively received, as many thought that working 24 hours continuously for one shift was excessive. On the other hand, physicians such as the Associate program director of the University of Nebraska surgery program feel that their learning is being compromised due to the restricted work hours, but also states "We all should be resident advocates, but at the end of the day, we're patient advocates. We need to find a happy medium between the two".[1]

The trigger for these newly implemented changes in the U.S training system can be credited to The Institute of Medicine of the National Academies (IOM). IOM is a non-profit committee in the U.S that conducts surveys and collects information from the public sector on how the healthcare system in the U.S can be improved. In 2007, the U.S Congress requested the IOM to investigate the work hours of junior doctors in the nation, and suggest changes that should be made based on the 2003 ACGME guidelines. In 2008, the IOM began their investigation, and much of their work revolved around three main concepts: preventing excessive fatigue, optimizing resident education and improving patient safety error and detection.[2]

Preventing excessive fatigue looked primarily at sleep patterns of residents. The guidelines suggested by the IOM

*Submission: 2012, May 15.*
*Accepted: 2012, July 19.*
*Process: Peer-Reviewed.*

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was that interns should not work more than 16 hours continuously, should have a set amount of time to sleep between shifts (preferably 8-10 hours, rather than the present 5 hours) and should not be allowed to work in addition to the 80 hours.2 Optimizing resident education was the key is to improve supervision of residents. IOM suggested that committees that overlook residencies (training programs) in their respective specialties should set a limit on the number of patients a resident can treat during a shift, which would then allow for the resident to have more spare time to improve their medical knowledge. Lastly, reducing patient error was investigated. The transfer of patient care between two physicians proved to be an issue. This is because transferring care, or "handovers", meant there was a higher risk for mistaken information to be conveyed to the receiving physician or a lack of communication, and therefore resulting in physician error.[2]

***Training as a Junior Doctor in the UK***

In the UK, the system implemented in August 2009 is based on the 48-hour/week guideline that is regulated by the Department of Health, and is known as the EWTD. In addition to working 48 hours a week, the guideline also states the following: A minimum daily consecutive rest period of 11 hours, a minimum rest break of 20 minutes when the working day exceed six hours, a minimum of four weeks' paid annual leave and a maximum of eight hours' work in any 24 hours for night workers in stressful job.[3]

There have been mixed reactions regarding the new guidelines for junior doctors, and recently the British Medical Association (BMA) conducted a survey with physicians regarding their opinion on the work directive. The survey was sent to over 3000 physicians who were members with the BMA, and the response rate was 16% (470 physicians).[3] The results were overall negative. In particular, only 20% of the respondents felt that the EWTD would improve patient care or safety, and over two-thirds believed it would have a negative effect on their training, believing 48 hours is not enough time to properly learn new skills and procedures.[3]

Before 2009, the workweek restriction was 56 hours. The survey included several comments about the new guidelines, some of them including: "48hr weeks mean more splitting of shifts which means more antisocial hours impacting on family life" or "48 hours is far too little hours to be adequately trained."[3] This is further evident in the following figure that shows over 66% want the BMA to become more involved and ensure that quality of training does not decrease, despite the new EWTD guidelines. The overall mood regarding the EWTD is clearly mixed, but seems to be that generally physicians are unhappy with the guidelines and feel that their training will be compromised in their given specialties.[3]

Dr. Peter Simpson, President of the Royal College of Anesthetists, gives an excellent analysis on how the EWTD will impact the training doctors as well as consultants in their specialty. He discusses the reduction in the number of hours is 75 to 100% less than what previous registrars would spend working in the same number of years, and therefore expresses concern that the new batch of anesthetist consultants will not be nearly as competent as the last generation.[4]

Professor Sir John Temple, the Chair and Research Development Council of the Healing Foundation, was requested by Medical Education England (MEE) to do an analysis on the EWTD and how it would impact training of junior doctors in the UK.[5] Sir Temple in his analysis came up with several points that demonstrate the improvements that can be made with the present working guidelines, as well as examining with specialties would be affected the most by the EWTD.[5] According to Sir Temple, acute hospital services particularly A&E would be most affected, due to the rising number of patients as well as the pressure to meet service targets, which is difficult to achieve when work hours are restricted.[5]

***Conclusion***

As a final year medical student in the UK, I have come across foundation year doctors who echo the sentiments described earlier in this reflection, as there is general dislike for the EWTD working rules. More importantly, I have come across consultants who are also unhappy with the EWTD, as a few of them have discussed how their training was far more rigorous in terms of hours, and therefore do not feel that the next generation of consultants will be as competent. In the US, I was engrossed in the healthcare system for over 4 months, which gave me an excellent view on structure of the training, as well as discussing with residents and consultants with regards to the ACGME guidelines. It is evident that both countries are amidst a transition period in their respective training systems for junior doctors, and hopefully over time each system will evolve and become a structure that is widely accepted and supported by the next generation of physicians.

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**Acknowledgements**

*I would like to thank my elective supervisors Dr. Susan Lerner and Dr. Rebecca Spanagel for helping me carry out this clinical work in the United States of America.*

**Conflict of Interest Statement & Funding**

*The Author has no funding, financial relationships or conflicts of interest to disclose.*

**Cite as:**

*Aiyer RS. A Reflection and Comparison of Physician Training in the United States of America and United Kingdom. Int J Med Students 2013;1(1):48-50.*

# Trauma Africa

Victor Y. Kong[1].

## The Experience.

"Major Trauma. Dr. Kong, please come to the Trauma Unit immediately. Dr. Kong, please come to the Trauma Unit immediately." Even though I have been working at Edendale Hospital as a trauma registrar for over a year, whenever I hear this announcement over the hospital intercom system, my heart beats just a little faster than normal. When I first arrived at Edendale my colleagues told me that the adrenaline rush I would experience after being called out to attend a new emergency would decrease over time, and indeed they were right. However, it is also true to say that on some occasions more than others, it is still felt more strongly than ever.

On one particular night, as I made my way towards the resuscitation area in response to yet another major 'trauma call', I was greeted by the most enthusiastic of paramedics, who was drenched in blood to the extent you would expect to see on the television drama Trauma. As we walked at a brisk pace, he started to tell me about the new case, "We have an unknown male with multiple GSWs to the abdomen, no recordable BP, and he is restless and hypothermic."The paramedic reported that the patient had been chased by the police and had been shot several times after having attempted a hijacking. In medical school there was a saying which went, "common things are common", and in some parts of South Africa crime is so rampant it is almost a daily occurrence. Faced with the prospect of treating this new 'unfortunate' victim, I tried to remain calm, especially when I saw that my best interns were struggling to obtain intravenous access. The stakes were high and everyone was watching and waiting for some sort of miracle to happen. The ATLS training doctors receive can sometimes give the impression that everything is supposed to work on the first attempt. For example, the 14G Venflon is supposed to somehow just slip into the antecubital fossa, without a hitch. Training is supposed to prepare doctors to manage these cases without even thinking about it. However, the golden rule of being a surgeon is always to have a Plan B (or even a Plan C) in these sticky situations. It takes a lot of discipline, training and experience to maintain a calm and composed exterior. When the resuscitation 'algorithm' began to tick for this patient, it became immediately clear to me that he needed an operation in order to survive. Without any intention of trying to impress the team, I quickly inserted a high flow femoral line and managed to start infusing a litre of Hartman's solution hanging by the patent's trolley. As the pump pushed fluid further into his vein, the rest of the resuscitation continued like clockwork. Then, when the patient was transfused, warmed and mostly awake, I signal led to the interns that it was time for them to move onto the next stage, and they knew exactly what I meant. One would come with me to the operating theatre, whilst the others would 'hold the fort' on the front line until I had finished with the patient. Interns seldom complain when I am on call because they know exactly what to expect and what is expected, which is to keep the patient alive by whatever means.

***Figure 1.*** *Typical Friday night scene ouside the trauma unit at Edendale Hospital, South Africa.*

Soon I was scrubbing up and donning that familiar blue gown in order to perform yet another trauma laparotomy. This was my seventh trauma laparotomy of the shift, and, in all honesty, I could hardly keep my eyes open because I had been operating in theatre literally all day and night. Just as I started to think, 'When will this shift ever end?' suddenly the adrenaline kicked in once more and I got even more excited. As cliché as it sounds, knowing that I can make a difference acts as a great motivator. More importantly, everything had been set up well by the team,

*What is a Registrar?*
**Registrar is the equivalent of Resident in North America. It means a surgeon still in training.**

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*Submission: 2012, March 8.*
*Accepted: 2012, May 19.*
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including the cell saver, fluid warmer and all the equipment needed for a trauma operation. Then, the Scrub Nurse greeted me with an ironic, "San'bonna" (Hello in Zulu) Dr. Kong – welcome back."

Without hesitation, I proceeded to follow a well practiced drill. I opened the abdomen in no time at all, and, as expected, blood was everywhere. It is strange that sometimes, for this operation, a surgeon's anxiety level seems to be inversely proportional to the number of swabs available to pack the abdomen. If swabs run out on a typically busy 'end-of-month-payday-Friday night' the next best option is to use sterile drapes, or whatever is available in the vicinity. All the basic manoeuvres I had been taught so well by my trauma consultants now came in handy. Of course, I thought, it is their shoes I ultimately want to fill, but for now I packedthe liver, the spleen was out, the stomach was repaired, and I made sure that the ends of the small bowel were stapled off properly. Just before the anaesthetist was about to tell me how much time had been wasted (as he always does), I managed to temporarily close the abdomen with a Bogota bag, and not one made in South America, but one made in Edendale hospital! I was in 'damage control mode' in order to keep the patient alive to fight another day. Again, it had been another exhilarating night. Nothing is more exciting than saving a life - this is why I became a surgeon.

Deciding to work as a Trauma Registrar at Edendale Hospital was one of the best career decisions I ever made. The trauma seen here is almost unimaginable in its volume, and it includes gunshots, stab wounds, and road traffic accidents, among many other things. At times you feel as if you are standing next to a surgical conveyer belt carrying extreme human suffering. However, on a positive note, most of the victims are young and fit and they usually have an extremely good outcome if their injuries are treated early. At EdendaleI get opportunity to hone my practical skills in a multitude of emergency procedures, including some that are seldom performed elsewhere in the world. No longer do I have to experience frustration in trying to compete with five other colleagues simply to insert a chest drain (the maximum any registrar has done in one shift was said to be around thirty!). Neither do I have to wait over six months just to be able to insert a central line because my anaesthesia colleagues 'need the experience for their log books'. Performing a venous cut down, cutting a surgical airway, or decompressing a tension pneumothorax, are some procedures you have to performroutinely in order to keep a patient alive. Just as a new intern is expected to be able to perform a phlebotomy as a standard skill, every trauma registrar at Edendale is expected to master complex skills quickly, and as routine. You simply have to be prepared to deal with whatever is presented to you, and, often, thepeople presented here on a daily basis are the sickest trauma patients. The most common operation performed at night is a trauma laparotomy, but more often, just like meeting a trajectory of bullets, it is difficult to know what type of case to expect next. From dealing with a minor serosal tear to treating a massive torrential haemorrhage which requires a combined laparotomy and thoracotomy, the cases seen here make life extremely exciting. Once, I vividly remember having to insert a chest drain (for a patient with massive haemothroax who was in extremis) in the corridor outside of the operating theatre when there was no more space left inside. Also, I remember performing an emergency cricothyroidotomy in a lift when it became stuck between floors. Luckily though, at Edendale the trauma consultants are among the best in the world and they are always available to help.

With trauma, no two patients are the same and everything appears as new. When I first performed a front room thoracotomy on a stab victim, I remember that when my

***Figure 2.*** *Entrance - Edendale Hospital.*


***Figure 3.*** *Emergency room thoracotomy for penetrating cardiac injury, traumatic arrest on arrival.*

hands were deep in his chest messaging his heart, I had the sensation that my own heart was beating far more vigorously than the pace at which I was trying to massage the patient's. However, emergency cases are what keep me, and many others, going through sleepless and lonely nights. At the end of the day, South Africa is one of the most dangerous countries in the world. When one of my consultants asked me why I had left a comfortable life in Dublin for a life in South Africa, I could not think of a perfect answer. Partly it was because I felt an urge to expand my horizons, and partly it was due to my sense of competition; I wanted to train myself to be as good as, or better than, my colleagues. Mostly though, it was in order to follow a desire that had been in my heart for many years, and to do this it seemed worth the risk. There are not many things worth risking one's life for, but to quench a thirst for a different type of surgical experience seemed worth the risk. Trauma surgery is definitely not for the faint hearted, but the experience I have gained at Edendale is invaluable; working at Edendale is the once-in-a-lifetime experience. I have matured far beyond my own expectations, and I have seen human suffering at the extreme end of the spectrum. I have learnt to become more compassionate for the less fortunate, and I have seen first-hand what extreme poverty means. Most importantly, I have learnt how to survive.

It takes a lot to try to remain strong in what is, at times, a potentially dangerous working environment, especially if you want to become the best surgeon. Sometimes, I wonder what life would have been like if I had not left for South Africa. At least I would not be hearing that one of my colleagues at another hospital has been stabbed to death by a patient. Or even worse, witnessing the distress of one patient shooting another patient in front of my eyes, an experience that left me paralysed with fear for days. However, it is more likely that I would be wondering what I was truly missing in my surgical career, which is the sense of excitement of trauma surgery. When I was writing up the operative notes for the gunshot victim, I recalled that only a short while ago another patient had been shot on the hospital premises right next to the ATM machine, and then, for a split second, I could have sworn I heard the sound of faint gunshots just outside of the hospital. Perhaps this was just cynicism, and tiredness at the end of a shift, but I reasoned that it would be far stranger not to be alert to the potential for danger after having experienced working at Edendale for over a year. However, before I even had time to let my imagination wonder further, the familiar voice on the hospital intercom system announced, "Major trauma. Dr. Kong, please come to the Trauma Unit immediately.' So, once again I made my way back to the Trauma Unit. This time, on my way back my anaesthetist approached me and said, "I hope you realise that your colleague has just booked in another three patients who all need trauma laparotomies. Are you still doing them or what?"As I was coming to the end of a long shift, it would have been easy

***Figure 4.*** *A: Patient with a stabbed abdomen, with bowel evisceration. B: Patient with multiple GSW (gunshot wound) to torso.*

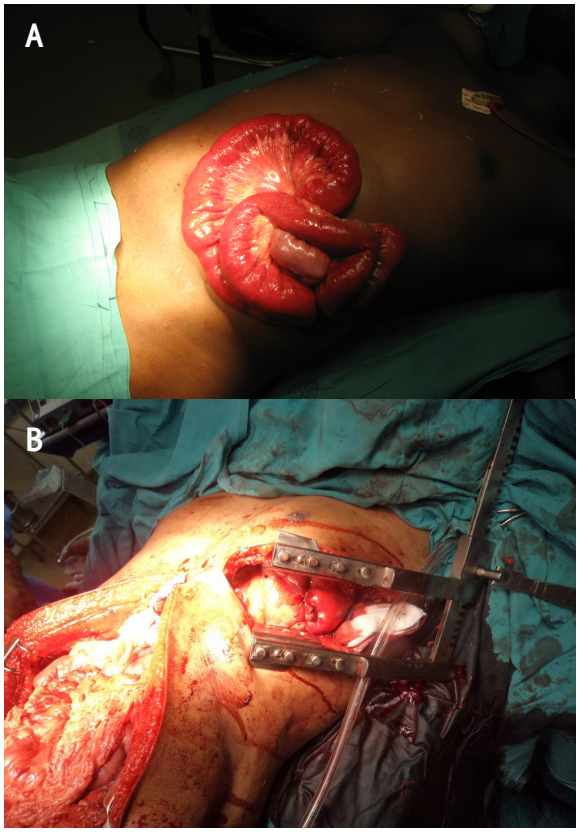


***Figure 5.*** *Me prior to performing a splenectomy (blunt trauma victum).*

to respond sharply to this type of comment, but instead, I composed myself once again and replied in a calm but assertive manner, "Yes I am, but not now. There is another trauma thoracotomy coming in first."

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

**Cite as:**
*Kong VY. Trauma Africa. Int J Med Students 2013;1(1):51-4.*

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|---|---|---|---|
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