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- Common ECG Lead Placement Errors. Part II: Precordial Misplacements.
- Medical Students' Knowledge and Attitudes Toward Female Sex Workers and Their Occupational Risk Factors.

- Penile Cancer in Cali, Colombia: 10 Years of Casuistry in a Tertiary Referral Center of a Middle-Income Country.
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## INTERNATIONAL JOURNAL *of* MEDICAL STUDENTS

### *International Journal of Medical Students*

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



### *Schisto SXies*

Sand Art. Scene from "Neglected: A Story of Schistosomiasis Infection in Ghana"

By Shelly Xie (with authorization).

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The *International Journal of Medical Students* is indexed or abstracted in: Biblioteca Virtual del Sistema Sanitario Público de Andalucía (BV-SSPA), Bielefeld Academic Search Engine (BASE), China National Knowledge Infrastructure (CNKI), CiteFactor, Copac, Dialnet, Directory of Open Access Journals (DOAJ), Directory of Research Journals Indexing (DRJI), Enhancing the QUALity and Transparency Of health Research (EQUATOR) Network, Genamics JournalSeek, Geneva Foundation for Medical Education and Research (GFMER), Google Scholar, Health InterNetwork Access to Research Initiative (HINARI), Healthcare Information for All (HIFA) Network, Index Copernicus (ICV 2012: 5.62), International Impact Factor Services (IIFS 2014: 1.212), J-Gate, Jour Informatics (Jour Info), JournalGuide, Journals Following the International Committee of Medical Journal Editors (ICMJE) Recommendations, JournalSeek, JournalTOCs, Mexican Index of Latin American Biomedical Journals (IMBIOMED), NewJour, Online Computer Library Center (OCLC) WorldCat, Open Academic Journals Index (OAJI), Open Science Directory, Research Bible, Scientific Indexing Services (SIS), Scientific Journal Impact Factor (SJIF 2012: 3.034), SHERPA/RoMEO, Strengthening the Reporting of OBservational studies in Epidemiology (STROBE Statement), The Open Access Digital Library, trueserials.com, Ulrich's International Periodical Directory, ZDB Database.

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e-ISSN 2076-6327 (Online)



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Issued in Rochester, MN, USA.

# International Journal of Medical Students

Year 2014 • Months Jul-Oct • Volume 2 • Issue 3

Int J Med Students. 2014 Jul-Oct;2(3)

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# The Quest for Quality Electrocardiographic Recording

Javier García-Niebla.<sup>1</sup>

For correct electrocardiography (ECG) diagnosis and interpretation, it is important not only to distinguish normal from pathological electrocardiograms, but also to ensure that they have been properly recorded.

Heden et al.,<sup>1</sup> reported that 2% of the 11,000 ECGs analyzed showed interchanged electrode placement. Thus, if 300 million ECGs are performed annually in the world, 6 million are erroneously recorded. This figure could even triple if one includes other frequent mistakes, such as vertical displacement of precordial electrodes and the distal placement of these on the limbs instead of the trunk.<sup>2</sup> Few manuals on electrocardiography have devoted space to warn about the effects of ECG recordings that do not conform to standards, but it seems that this is changing.<sup>3</sup>

This issue of the Journal contains two interesting articles by Rosen et al., who form part of the research group led by Dr. Adrian Baranchuk, which address the most common mistakes made in daily practice in relation to improper placement of limb and precordial electrodes, as well as tell-tale signs for their detection.<sup>4,5</sup>

In this editorial we will elaborate on certain issues directly related to possible errors on performing an ECG.

## Is it important to prepare the patient for an ECG?

Yes. Patients must be informed of the procedure to be performed, emphasizing that it is painless and harmless but they must lie still, breathe normally and refrain from talking. Nervousness and sweating are to be resolved before starting the procedure. Proper skin preparation, with shaving if necessary, is required to reduce impedance and ensure adhesion of the electrode. This greatly helps to minimize the appearance of artifacts that can sometimes cause significant diagnostic errors.<sup>6</sup>

## Is it easy to identify ECG patterns obtained with reversal of limb electrodes?

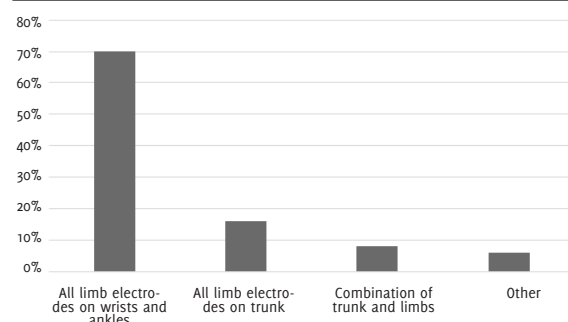
Yes. They are generally easy to identify. Only one pattern, resulting from the reversal of left arm and left leg electrodes, may be easily overlooked, even by experts. The presence of a P wave in lead I with greater amplitude than that in lead II and a positive terminal P wave morphology (-/+) in lead III can

sometimes alert us to this error.<sup>7</sup> Given the low specificity of these criteria, it is advisable to check for this error and repeat the ECG to ensure correct electrode placement.

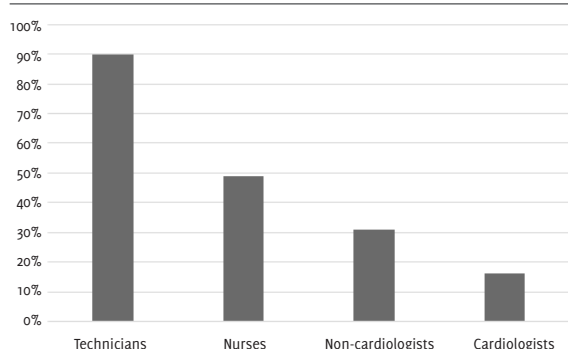
## Can limb electrodes be placed on the trunk?

No. Proximal placement of limb electrodes or their placement on the trunk is not compatible with a standard ECG.<sup>8</sup> The advent of easily applicable adhesive electrodes with decreased muscle noise has favored this practice (**Figure 1**).<sup>9</sup> ECG changes are clearly visible when limb electrodes are placed on the trunk. In these cases, there is a QRS axis deviation to the right, which decreases the voltage of the R wave in leads I and aVL and increases it in leads II, III, and aVF. In a patient with necrotic Q wave in leads II, III and aVF, placing limb electrodes on the trunk may reduce both the voltage and the duration of the

**Figure 1.** Frequency of incorrect limb electrode placement.<sup>9</sup>



**Figure 2.** Proportion of professionals who correctly positioned the V1 electrode (adapted from Rajaganesan et al.).<sup>14</sup>



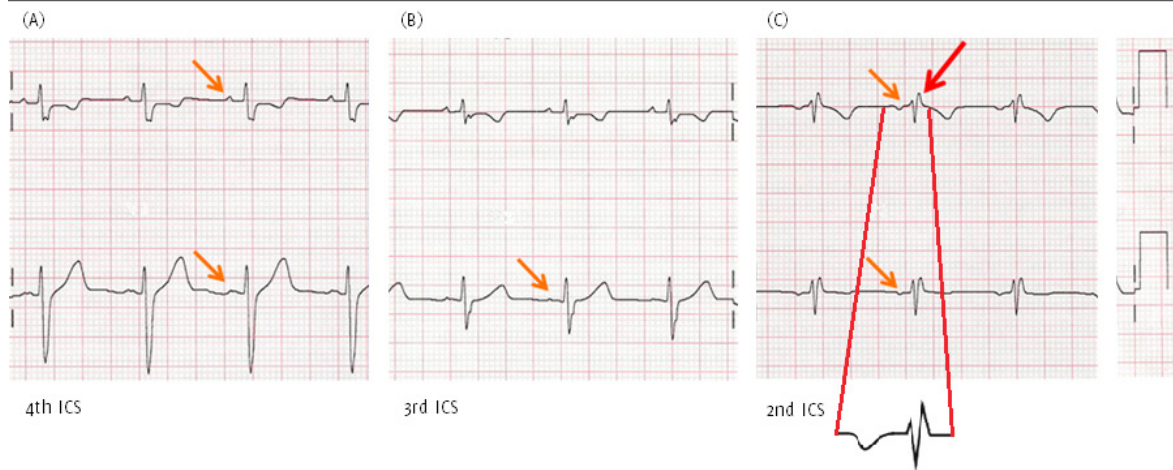
**About the Author:** Javier García Niebla is a registered nurse with a degree in Nursing from the University of La Laguna and an associate lecturer at the University School of Nursing, Hospital "Ntra. Sra. de La Candelaria". For almost six years he directed the webpage of the Spanish Association of Nursing in Cardiology. As an investigator and author, he has published in dozens of scientific journals in the field of cardiology and is a recognized expert in electrocardiography, and a regular collaborator of Prof. Antoni Bayés de Luna.

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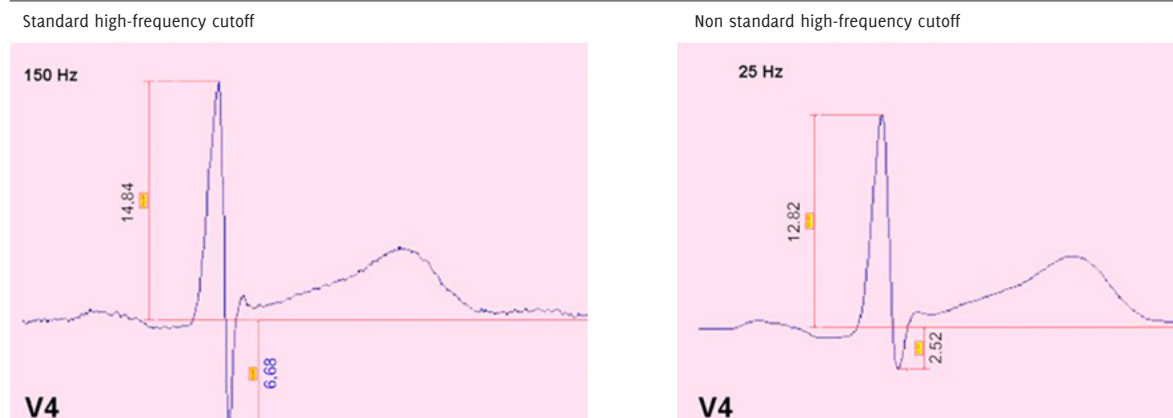
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**Figure 3.** The P wave is positive in V1-V2 (arrows) when the electrodes are correctly placed (A) on the 4th intercostal space (ICS). When V1-V2 electrodes are misplaced on the 3rd ICS (B), the low-voltage or flattened P wave in V2 (arrow) is the tell-tale sign of high placement. And when the V1-V2 electrodes are misplaced on the 2nd ICS, one sees a negative P wave and rsR' (red arrow) which indicate high placement of the electrodes (C).



**Figure 4.** Effect of a high-pass filter in lead V4. Note how the voltages of the R wave (14.84 mm to 12.82 mm) and the S wave (6.68 mm to 2.52 mm) are reduced when applying a non-standard 25Hz filter.



wave. If for any reason we need to perform the ECG with this non-standard placement (a patient with Parkinson's, for example), this should be expressly recorded in writing and taken into account in the interpretation.

#### Is it necessary to place the precordial electrodes exactly on their established sites?

Yes, precordial lead electrodes must be placed exactly on their specific internationally established anatomical locations.<sup>10</sup> Several published studies have described the ECG changes that occur when the electrodes are misplaced.<sup>11,12</sup>

#### Do professionals who regularly perform ECG demonstrate better electrode placement?

No. Even technicians with an average of 15 years or more experience and who perform over 30 ECGs a day can make important mistakes.<sup>11</sup> However, their theoretical knowledge about precordial lead placement is superior to that of other professionals (Figure 2).<sup>13</sup> The most common mistakes include:

- A) High placement of V1-V2.
- B) V5-V6 placed too low in some cases or located along the curvature of the 5th intercostal space.

#### Once the ECG has been obtained, what are the tell-tale signs of high V1-V2 placement?

Three morphologies help identify high placement of these electrodes (Figure 3)<sup>14,15</sup>:

- a) a negative P wave in V1 only. Under normal conditions, the P wave in V1 is positive or biphasic +/-, more positive than negative with a mild slope.
- b) The rsR' morphology with a negative P wave is exclusive to ECGs recorded with high placement of the V1 electrode on the 2nd intercostal space. It is seen in 17% of cases of inappropriate placement in healthy individuals.
- c) A negative component of the P wave or a flattened P wave in V2 are indicators of high placement.

High positioning of the electrodes V1-V2 can mimic a Brugada type 2 pattern. However the r' in this case is narrow with the base of the lower triangle measuring less than 4 mm.<sup>16,17</sup>

#### Can ECG filter settings affect the ECG?

Yes. When filters are applied to prevent unwanted noise and obtain better quality recording of the cardiac signal, the ECG can sometimes be markedly affected unless the recommended cutoffs are applied:

### *Muscle noise filter*

If the cutoff is too low, signals which are important from the clinical point of view can be eliminated (pacemaker spikes, amplitude of the R wave, QRS notches, etc.) (**Figure 4**).<sup>18</sup> The cutoff frequency should be at least 150 Hz in the case of adults and adolescents and up to 250 Hz in the case of children.

### *Baseline filter*

It is important to remove the noise generated by a wandering baseline which may occur as a result of small movements and breathing of the patient. Inadequate filter application can result in significant distortion of the ST segment and T wave, simulating acute coronary syndrome or Brugada syndrome.<sup>19</sup> The recommended cutoff is 0.05 Hz, increasing up to 0.67 Hz if linear filters with zero phase distortion are used.

### *How can we reduce the number of errors?*

In view of the above considerations, it is necessary to promote specific training programs and refresher courses on the performance and interpretation of ECGs, based on the latest recommendations made by the major international scientific societies. These should include the correct placement of the electrodes, assimilating the significance of correct technique, the reading of normal and pathological patterns, together with a specific focus on recognizing ECG patterns resulting from improper positioning of electrodes, the identification of artifacts and other technical problems that could lead to misinterpretation.

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### Acknowledgments

None.

### Conflict of Interest Statement & Funding

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

### Cite as:

García-Niebla J. The Quest for Quality Electrocardiographic Recording. *Int J Med Students*. 2014 Jul-Oct;2(3):87-9.



# Writing a Case Report: A Work of Art

Christian Ortega-Loubon,<sup>1</sup> Ricardo Correa-Márquez.<sup>2</sup>

Case reports are a time-honored, important, integral, accepted work, firmly established within the medical literature, and represent a growing importance of valuable clinical medical information.<sup>1</sup> Parkinson's disease, and Kaposi's Sarcoma are only two examples of famous diseases first described in the case report format, making us acknowledge the value of case reports to the scientific literature. Case reports are valuable resources of new and unusual information that may lead to vital research and advances in clinical practice that improve patient outcomes.

Despite the fact that it lies at the bottom of the evidence based classification, the value and contribution of case reports to the advancement of medicine is huge. This will continue in the future. There are 190.703 citations with the term of "case report" up until November 2012 in PubMed database, and in 1 year the number grew to 200.737 (PubMed, Available from: <http://www.ncbi.nlm.nih.gov/pubmed>, cited 2013 November 30). This means that in only 1 year there are more than 10.000 case reports published in the database. This huge number of citations shows that case reports have contributed a big proportion of medical literature and grow rapidly over time.<sup>2</sup>

This is because published case reports provide essential information for optimal patient care because they can describe important scientific observations that are missed or undetected in clinical trials, and provide individual clinical insights thus expanding our knowledge base and giving birth to new research lines. Information strays from the classical textbook case, leading to a better and safer patient care.

The reason is that the human being has many features that make it wonderful: it has a complex anatomy and physiology, communication skills, intelligence, imagination, emotion, and most surprising is the fact that each of us is unique, as a product of a harmonious genetic and environmental interaction. Doctors treat patients, not diseases.<sup>3</sup>

The act of recording, discussion with colleagues, and publishing our clinical observations with patients remains essential to the art of medicine and patient care. As Osler once said "Always note and record the unusual...Publish it. Place it on permanent record as a short, concise note. Such communications are always of value."<sup>4</sup>

Few if any have had formal training on what constitutes a good

case report and how to write one. Unlike many other aspects of our medical training, that of writing case reports is not standardized. There is a wide body of published literature on how to construct a case report, including the different sections of a case report and when to write one, but different journals have different criteria and case report quality can be variable. We made an effort trying to accomplish this by writing the book "Case Reports: Semiology and Publication" (in spanish: Casos Clínicos: Semiología y Publicación), looking for standardize the form of how to make, present at a medical congress, and even publish a case report.

There are guidelines for different publication types: randomized controlled trials (Consolidated Standards of Reporting Trials, or CONSORT), observational studies (Strengthening the Reporting of Observational studies in Epidemiology, or STROBE), and systematic reviews and meta-analyses (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, or PRISMA); guidelines have also been developed for adverse-event case reports, and all authors should be familiar with the Committee on Publication Ethics (COPE) and the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network. But, it was not until September 2013, that an international reporting guideline for case reports (CARE) was presented. It will provide an international, general, non-journal-specific framework for completeness and transparency for published case reports, striking a balance between adequate detail and concise writing that can be used by all authors for all journals that publish case reports.<sup>5</sup>

The CARE guidelines consists of a checklist that comprises 13 primary items to include when writing a case report: title, key words, abstract, introduction, patient information, clinical findings, timeline, diagnostic assessment, therapeutic interventions, follow-up and outcomes, discussion, patient perspective, and informed consent (CARE Guidelines, Available from: <http://www.care-statement.org/care-checklist.html>, cited 2014 July 30).

Every case report is divided into five sections: abstract, introduction, case presentation, discussion and conclusion. The abstract briefly summarizes the case and its clinical relevance. It should clearly state the subject and educational value of the case report to introduce the readers to the central theme of the article. Writing the abstract is easy after the whole text is written. It is important because it gives information about

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what the article is about, and its availability will allow for easier retrieval from electronic database and help researchers discern their level of interest in the manuscript. The Introduction should be concise and immediately attract the attention and interest of the reader. It should provide the important information of the case report, background, epidemiologic data and novelty of the case report. In this section, make the case worthy to be published to the readers of the journal.

The case presentation should describe the patient's story in chronological order and in enough detail for the reader to establish his or her own conclusions about the case's validity. It should include information that pertains to the case with a clinical teaching point, and avoid confusing, irrelevant and superfluous data. The patient demographics such as age, sex and race must be included.

The discussion section is the most important section of the case report. It is the selling point that makes the article worth publishing. It should evaluate the patient's case for accuracy, validity, and uniqueness; compare and contrast the case report with the published literature; derive new knowledge; summarize the essential features of the report; and draw recommendations. The conclusion section should be brief and based on the evidence reviewed in the discussion section, and emphasize its applicability to practice. The author may suggest that clinicians be aware of the insight learned from the case or suggest heightened vigilance, prudent management, avoidance, further study before taking action, or new ideas for investigation.<sup>6</sup>

Last, the author must choose an interesting title. It is very important because many readers screen articles looking only at the title. We suggest developing the title after writing the whole text to see what have been discussed predominantly in the article.

Early case reports were anecdotal reportings about a novelty disease. However, a truly unique case is a rare event in clinical practice, and by focusing solely on novelty, many authors de-emphasize the educational value of their reports. Cases that increase the awareness of an unusual condition, describe a rare presentation of a common condition, describe diagnostic errors, their causes and consequences, rebut an accepted theory, or identify innovative treatment and diagnostic strategies are valuable additions to the medical literature whether they are novel or not.<sup>3,7</sup>

Writing case reports need academic and clinical skills, along with a sense of art to interest the editor to publish and the readers to read and study about the case we report. It is a combination between writing with academic knowledge and logical thinking, and art to interest people, or make colleagues want to know more and study about that special case report. Like any other literature is a work of art, a case report is also an art. Given the broad range of topics that can be legitimately highlighted in a case report, every one during their medical career can write a case report. It offers an excellent opportunity to gain experience in scientific writing, which will keep improving with the articles you will write. This practice of continuous writing will help you discover the skills necessary to make any manuscript you write worth publishing to any journal submitted.

It is the teaching point that makes case reports worth publishing, so every clinician and academic professional who wants to published case report must show the novelty and teaching point to the editors and readers. Every author of a case report must focus on why is the case important for the reader, why the report should be published, and who will read it.<sup>2</sup>

Writing a case report can be difficult for several clinicians or lecturers, even though they are experienced clinicians. We hope to encourage authors to write and submit manuscripts. By writing case reports, they will build their own clinical reasoning about patients and also sharpen their clinical instinct.

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## Acknowledgments

We would like to thank Francisco Javier Bonilla-Escobar, Editor in Chief of IJMS, for the invitation to write an Editorial to the Journal regarding our experience on Writing Case Report.

## Conflict of Interest Statement & Funding

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

## Author Contributions

Conception and design the work/idea: COL RCM. Write the manuscript: COL RCM. Critical revision of the manuscript: COL RCM. Approval of the final version: COL RCM.

## Cite as:

Ortega-Loubon C, Correa-Marquez R. Writing a Case Report: A Work of Art. *Int J Med Students.* 2014 Jul-Oct;2(3):90-1.

# Common ECG Lead Placement Errors. Part I: Limb lead Reversals

Allison V. Rosen,<sup>1</sup> Sahil Koppikar,<sup>2</sup> Catherine Shaw,<sup>3</sup> Adrian Baranchuk.<sup>3</sup>

## Abstract

**Background:** Electrocardiography (ECG) is a very useful diagnostic tool. However, errors in placement of ECG leads can create artifacts, mimic pathologies, and hinder proper ECG interpretation. It is important for members of the health care team to be able to recognize the common patterns resulting from lead placement errors. **Methods:** 12-lead ECGs were recorded in a single male healthy subject in his mid 20s. Six different limb lead reversals were compared to ECG recordings from correct lead placement. **Results:** Classic ECG patterns were observed when leads were reversed. Methods of discriminating these ECG patterns from true pathologic findings were described. **Conclusion:** Correct recording and interpretation of ECGs is key to providing optimal patient care. It is therefore crucial to be able to recognize common ECG patterns that are indicative of lead reversals.

**Keywords:** Cardiology, Electrocardiography, Medical Errors, Limb Lead Reversal, Medical Education (Source: MeSH-NLM).

## Introduction

Electrocardiography (ECG) remains a very useful diagnostic tool in the 21st century.<sup>1</sup> In this clinical era, it remains one of the most useful diagnostic tools in medicine.<sup>2</sup> It is both inexpensive and very efficacious in many different clinical scenarios. However, proper ECG recording is of utmost importance in order to ensure an accurate interpretation of findings.<sup>3</sup> Due to the structure of different healthcare programs, ECGs may be recorded not by expert technicians, but by whoever is available.<sup>4-6</sup> This has led to multiple errors in interpreting results.<sup>7-10</sup> Erroneous interpretation of ECGs has led to improper treatment of patients.<sup>11,12</sup> Prior work has identified some common ECG placement errors and their resulting artifacts.<sup>13</sup> The REVERSE mnemonic is a useful tool that can be used to identify abnormal electrocardiographic findings and the common placement errors that can elicit such findings (Table 1).<sup>7</sup>

The purpose of this study is to review some of the most common recording errors. For the purpose of clarity, this work has been divided into two parts. Part 1 is dedicated to limb lead reversals. Part 2 will deal with precordial placement errors.

## Methods

A 24-year-old healthy male on no medications, and with no medical conditions, served as a model for ECG recordings. Recordings were obtained with the help of an expert technician (CS). A 12-lead ECG (General Electric, Mac 5500, United States) set up at 150 Hz, 25.0 mm/s, and 10.0 mm/V was taken in a normal supine position. Arm electrode placements were selected in accordance with the AHA recommendations (Figure 1).<sup>14</sup> A series of lead reversals were conducted in order to recreate these classic patterns.

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**Table 1.** REVERSE mnemonic: an easy approach to remember the most frequent causes of electrocardiographic placement errors and artifacts.<sup>7</sup>

	Abnormal Finding	Significance
<b>R</b>	R wave is positive in lead aVR (P wave also positive)	Reversal of left arm and right arm electrodes
<b>E</b>	Extreme axis deviation: QRS axis between +180° and -90° (negative R wave in lead I, positive R wave in aVF)	Reversal of left arm and right arm electrodes
<b>V</b>	Very low (<0.1 mV) amplitude in an isolated limb lead (isolated "flat" lead)	Reversal of right leg and left arm or right arm electrodes
<b>E</b>	Exchanged amplitude of the P waves (P wave in lead I greater than in lead II)	Reversal of left arm and left leg electrodes
<b>R</b>	R wave abnormal progression in the precordial leads (predominant R wave in V1, predominant S wave in V6)	Reversal of precordial electrodes (V1 through V6)
<b>S</b>	Suspect dextrocardia (negative P waves in lead I)	Reversal of left arm and right arm electrodes
<b>E</b>	Eliminate noise and interference (artifact mimicking tachycardias or ST-T changes)	

Source: Modified from Baranchuk A, Shaw C, Alanazi H, et al. Electrocardiography pitfalls and artifacts: The 10 commandments. Crit Care Nurse. 2009;29(1):67-73. Copyright © 2009. Reprinted with permission from the corresponding author (AB).

Submission: Jun 27, 2014  
Acceptance: Sep 3, 2014  
Process: Peer-reviewed

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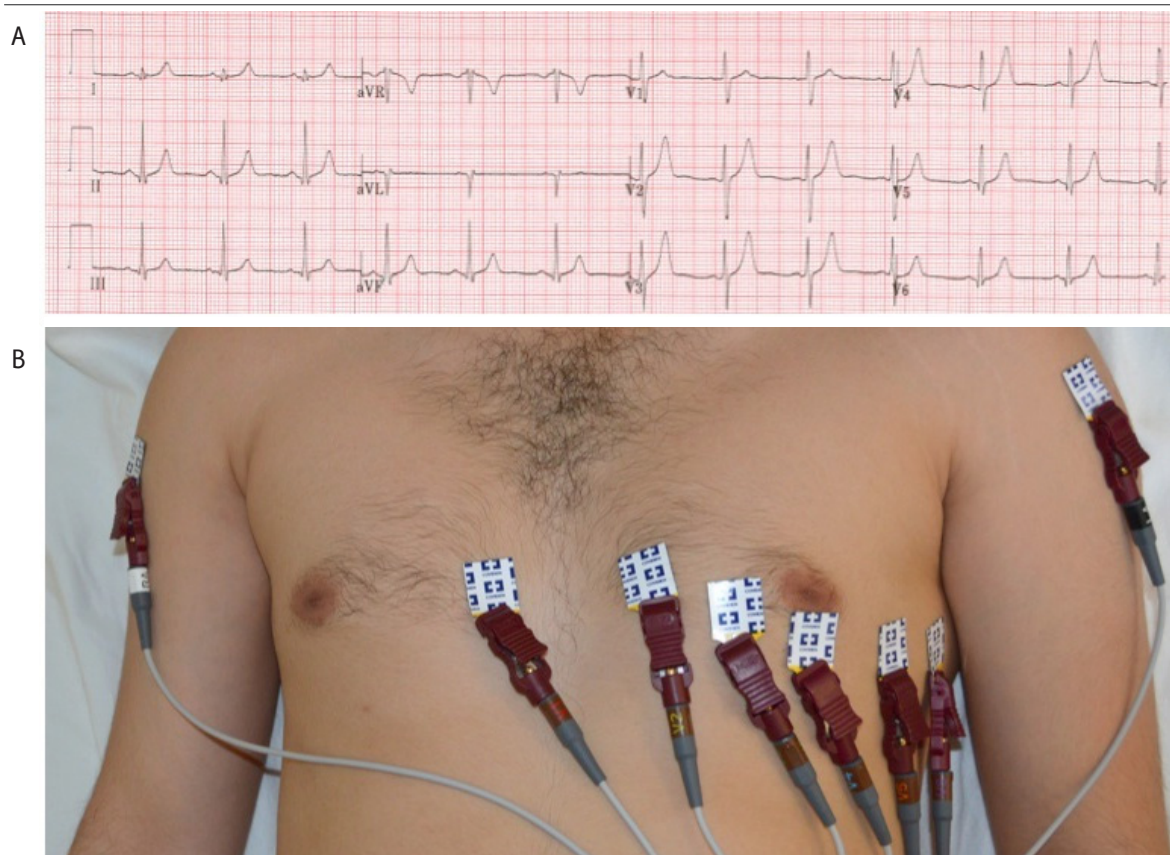
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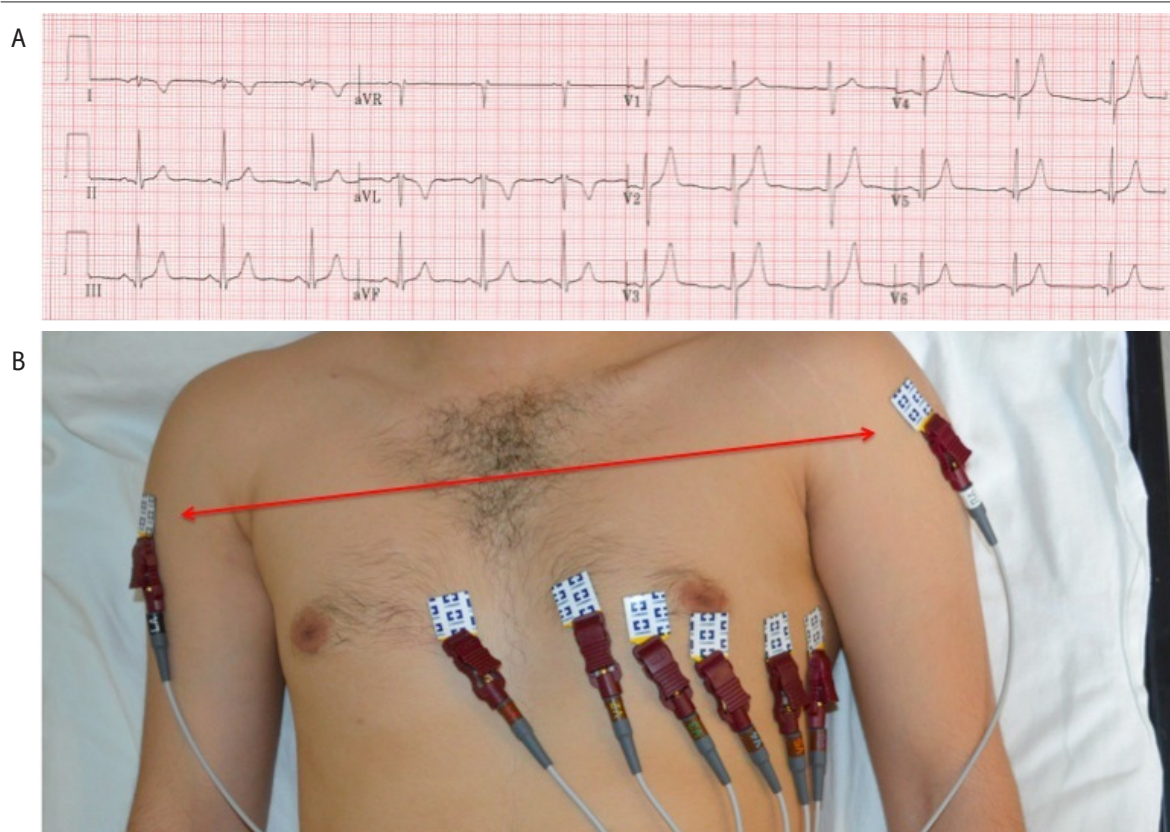
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**Figure 1.** 12 lead ECG depicting correct lead placement. (A) ECG recording. (B) Correct lead placements on chest and arms.



**Figure 2.** 12 lead ECG depicting left arm and right arm reversal. (A) ECG recording. (B) Arrows point to reversal of leads on left arm and right arm.





## Results

### Left Arm and Right Arm Reversal

Reversal of the arm electrodes is a common error.<sup>15</sup> This produces a reversed P wave, QRS complex, and T wave in leads I and aVL (Figure 2). These findings can mimic an ectopic atrial rhythm, however, the inverted P waves should not be followed by QRS inversion in ectopic atrial rhythms. In the case presented here, the negative polarity of the QRS and T wave ruled out ectopic atrial rhythm.<sup>16</sup> Inversion of P waves and QRS complexes in leads I and aVL can also be misinterpreted as dextrocardia. Dextrocardia can be ruled out as a diagnosis by noting normal R wave progression in the precordial leads in the context of an arm reversal. Dextrocardia will typically present with poor R wave progression in the precordial leads, as ventricular depolarization occurs in the opposite direction.<sup>7,15</sup>

### Left Leg and Right Leg Reversal

Reversal of the leg leads does not produce a significantly altered ECG, as seen in Figure 3. It has therefore been hypothesized that this error goes unrecognized in many cases.<sup>15,16</sup>

### Left Arm and Left Leg Reversal

Reversal of the left limb leads can create subtle changes that are easily missed.<sup>16</sup> This reversal results in Einthoven's triangle rotating 180 degrees vertically around an axis formed by aVR. Therefore, a left arm and left leg reversal can be confirmed if the P wave amplitude is greater in lead I than in lead II and/or a positive component of the terminal P wave is observed in lead III (Figure 4). This finding is known as the "Abdollah sign".<sup>7,17</sup>

### Left Arm or Right Arm and Right Leg Reversal

If a reversal involves the right leg and one of the arms, the potential difference recorded between the legs will be zero.<sup>7</sup> This results in a "flat-line" or pseudoasystole of an isolated lead. Reversal of the left arm and right leg will result in pseudoasystole in lead III (Figure 5).<sup>15,16</sup> Similarly, reversal of the right arm and right leg results in pseudoasystole in lead II (Figure 6).<sup>7,8,15</sup>

The presence of low voltages in the limb leads could suggest a diagnosis of anything that "dampens" the reading between the heart and a recording electrode, such as a pericardial effusion or amyloidosis. However, low voltages in all the leads are required for such a diagnosis. In the case presented here, while there are low amplitudes and voltages, they are isolated to one limb lead. Furthermore, the precordial leads are all normal, making a lead reversal the most likely diagnosis.<sup>8</sup>

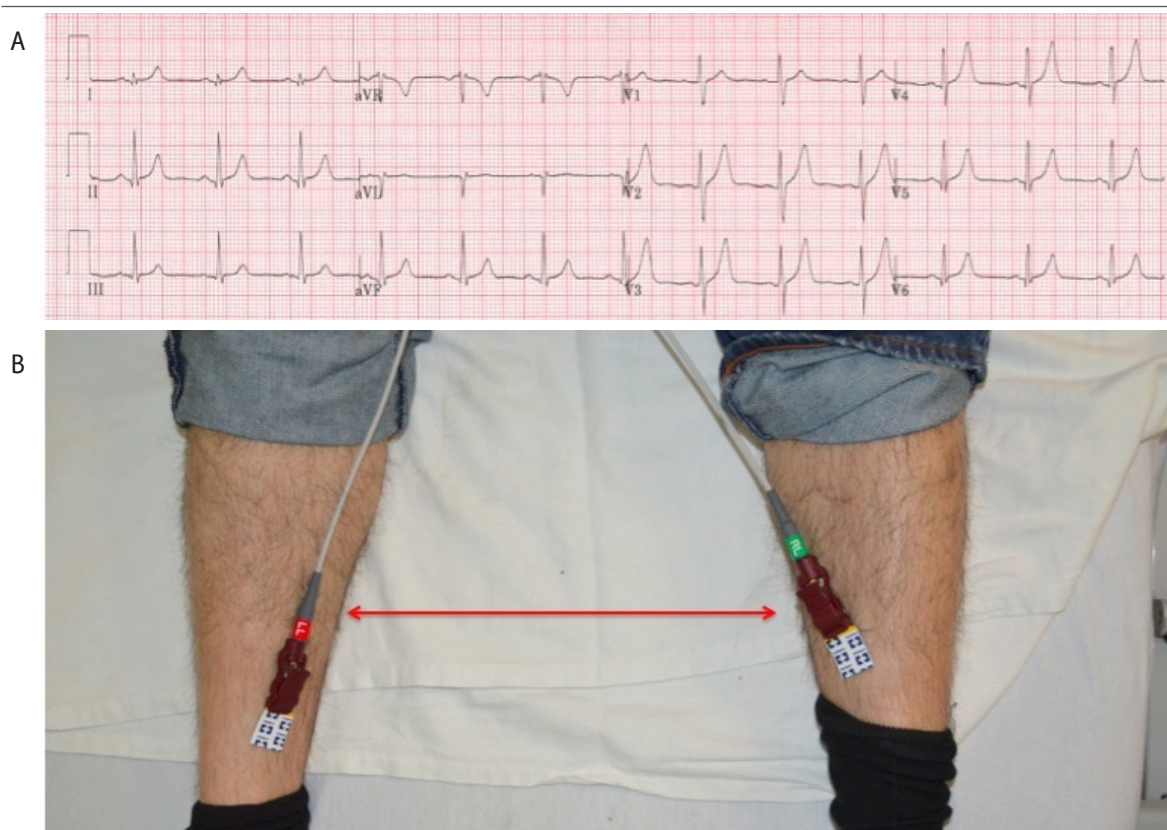
### Right Arm and Left Leg Reversal

Reversal of the right arm and left leg electrodes produces a generalized inversion of all the frontal plane leads (I, II, III, aVF) except aVL. Furthermore, lead aVR is upright. This recording can closely mimic a chronic phase inferior myocardial infarction due to inverted T waves and QS complexes in leads II, III and aVF (Figure 7). However, a high index of suspicion is required to detect lead reversal, as lead I and aVR will not be inverted from baseline in an inferior myocardial infarction.<sup>18</sup>

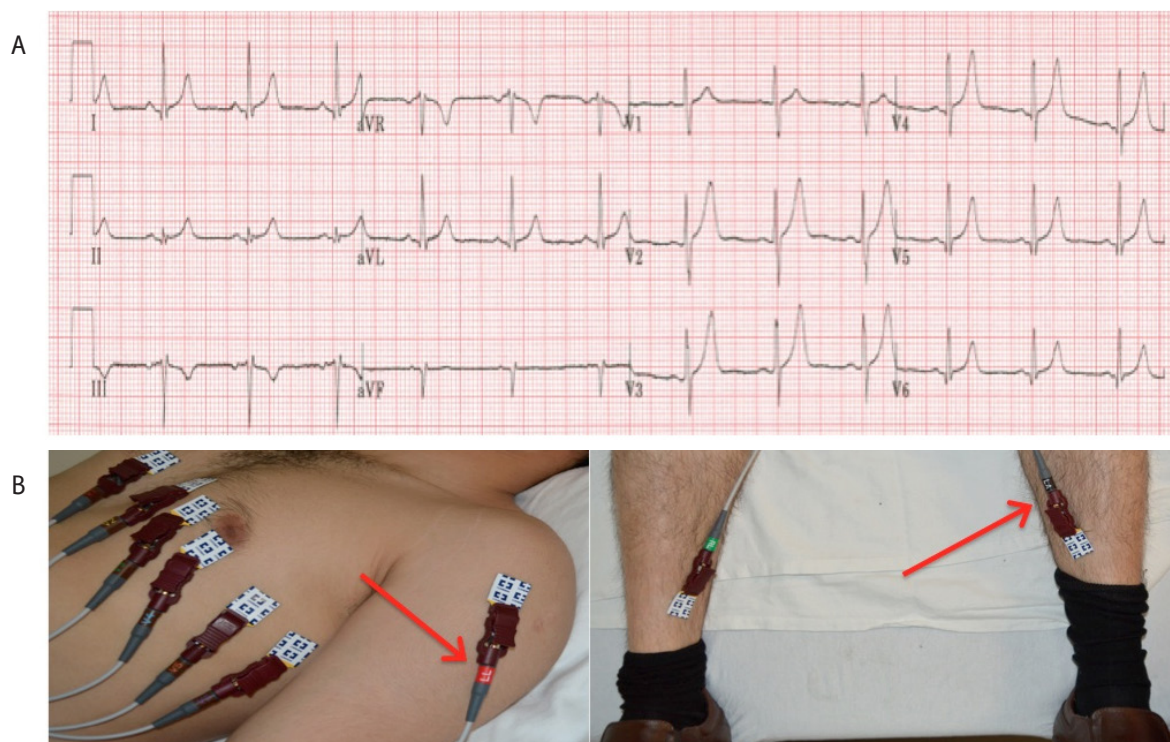
### Dual-Lead Reversal

Reversal of right arm with right leg, and left arm with left leg can have several physiologic mimics (Figure 8). The low voltage

**Figure 3.** 12 lead ECG depicting left leg and right leg reversal. (A) ECG recording. (B) Arrows point to reversal of leads on left leg and right leg.



**Figure 4.** 12 lead ECG depicting left arm and left leg reversal. (A) ECG recording. (B) Arrows point to reversal of leads on left arm and left leg.



in the limb leads is suggestive of a pericardial effusion. However, the precordial leads are normal, making this diagnosis less likely.<sup>19</sup> Low atrial rhythm might similarly be suspected due to inverted P waves in leads II, III and aVF. However, the diagnosis of low atrial rhythm further relies on QRS complexes being usually upright in the inferior leads along with upright P waves in aVR. In this case, although P wave inversions are present in the inferior leads, the other electrocardiographic findings are absent, suggesting that it is unlikely to be a low atrial rhythm.<sup>20</sup> As discussed previously, a differential diagnosis of dextrocardia can be eliminated due to normal R wave progression in the precordial leads.<sup>7,15</sup>

The ECG of a dual-lead reversal can be identified by several findings. These findings are a result of a complete reversal of the Einthoven triangle.<sup>8</sup> Firstly, inversion of P waves and QRS complexes can be seen in the three inferior leads (II, III and aVF). The reversal also leads to an upright QRS complex in aVR mimicking a false left-axis deviation. Lastly, low voltages are seen in the limb leads, but not in the precordial leads. One may rule out a left arm and left leg exclusive reversal through the absence of the Abdollah sign, and a right arm and right leg exclusive reversal through the absence of pseudoasystole in lead II.<sup>8,21</sup>

## Discussion

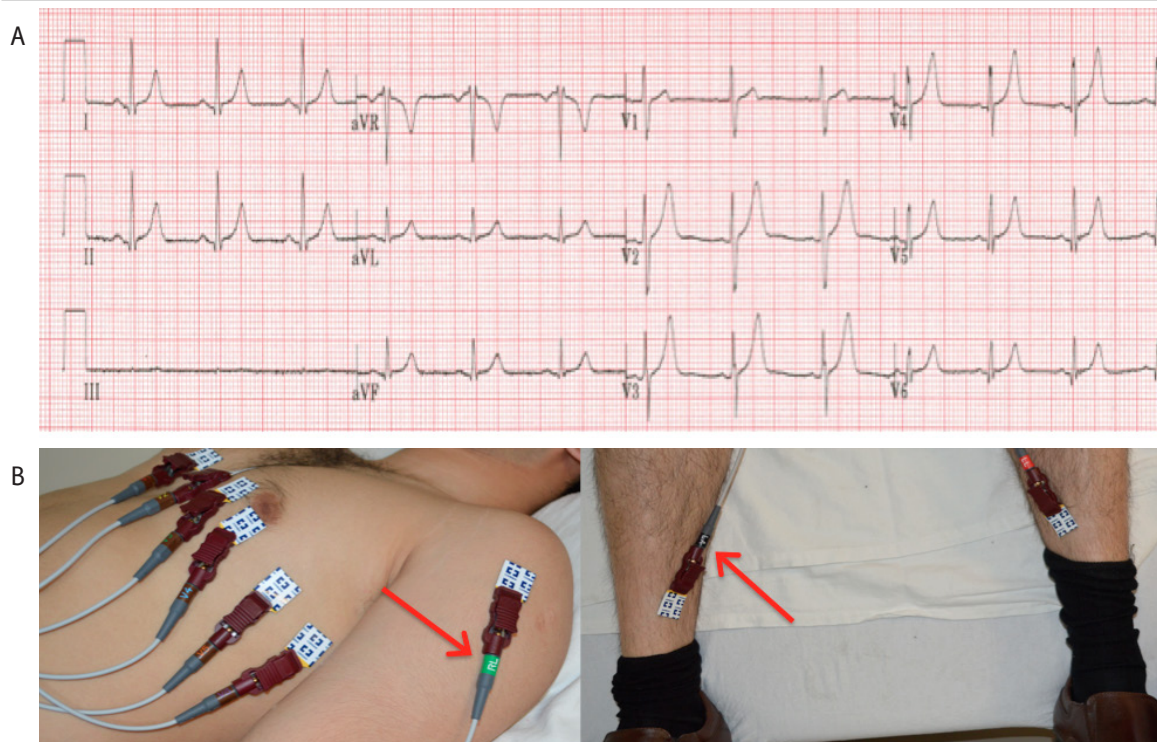
Proper ECG recording facilitates appropriate interpretation and diagnosis. Electrode misplacements can lead to morphological changes on ECG that could potentially be interpreted as ischemic or arrhythmic in origin. Therefore, recognition of the patterns seen in improper lead positioning is essential to avoid incorrect diagnoses and unnecessary treatments.<sup>11,22,23</sup>

Electrode misplacements are a relatively frequent finding, present in 0.4% of ECGs done in outpatient clinics, and even more common at 4% in intensive care units.<sup>7</sup> Several key findings on an ECG can help clinicians identify potential signs of electrode misplacements. In order to systematically identify these telltale clues, mnemonics to remember common errors and recognize their findings have been previously proposed. The REVERSE mnemonic is one such tool that outlines the most frequent abnormal findings on ECG (*Table 1*).<sup>7</sup> Of note to our cases, three common limb lead reversals are identified in the mnemonic; (1) reversal of the left arm and right arm electrodes, (2) reversal of the right leg electrode with either of the arms, and (3) reversal of the left arm and left leg electrodes. The relevant abnormal findings on ECG have been previously explained in the results and are summarized in the table. The mnemonic also helps identify other common pitfalls in ECG recordings such as reversal of precordial leads and interference artifacts. With this mnemonic, a careful and systematic examination of ECGs will help rule out potential problems with the recording. Interestingly, although placement errors can mimic pathologies, pathologies exist that can also mimic placement errors.<sup>24</sup> This further emphasizes the importance of careful interpretation of ECGs. Continued efforts to actively recognize lead reversals may help to avoid medical errors in diagnosis and treatment.

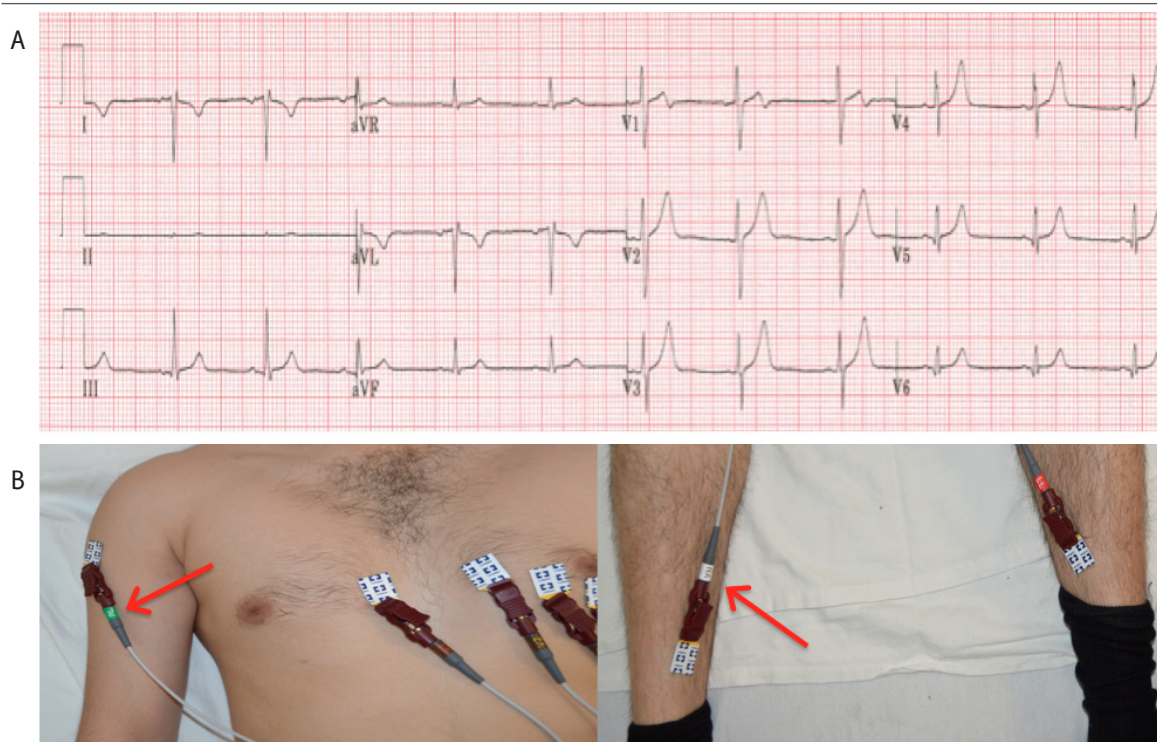
In conclusion, the ECG continues to be one of the most useful diagnostic tools in modern medicine. Health care providers initiate therapy based on the appropriate interpretation of ECGs. Systematic recognition of common ECG placement errors will help clinicians avoid unnecessary therapeutic interventions and enable them to obtain a properly recorded ECG.



**Figure 5.** 12 lead ECG depicting left leg and right leg reversal. (A) ECG recording. (B) Arrows point to reversal of leads on left leg and right leg.

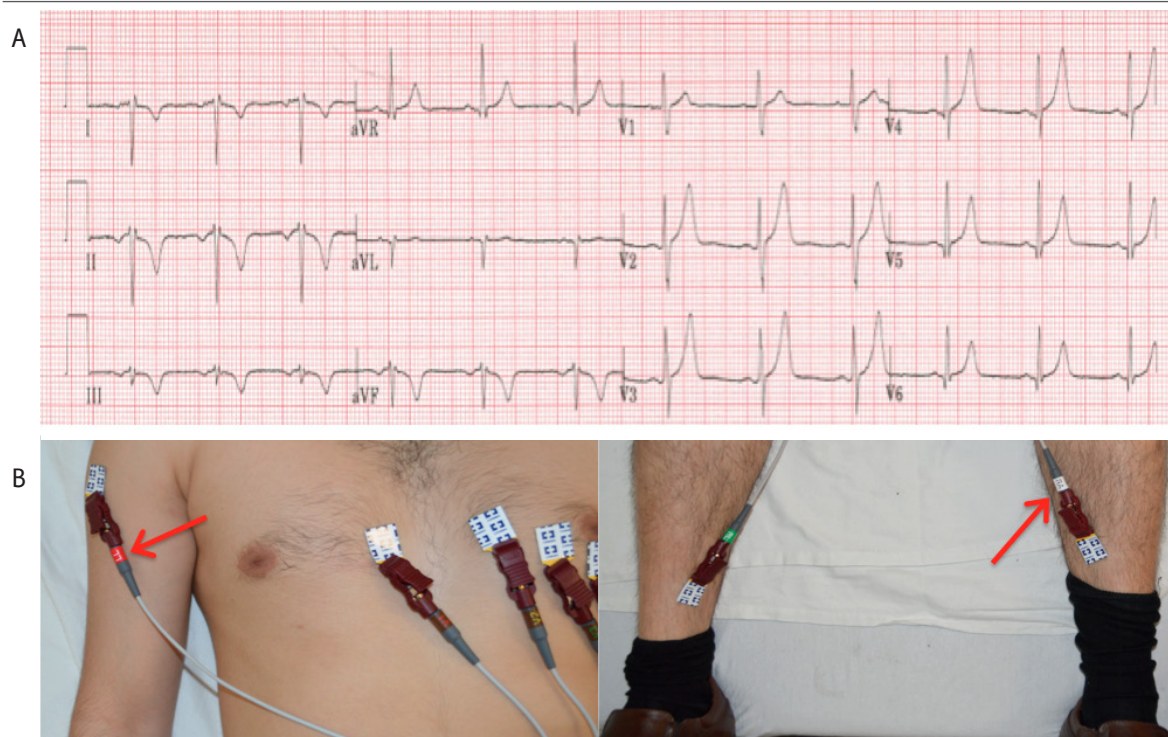


**Figure 6.** 12 lead ECG depicting right arm and right leg reversal. (A) ECG recording. (B) Arrows point to reversal of leads on right arm and right leg.

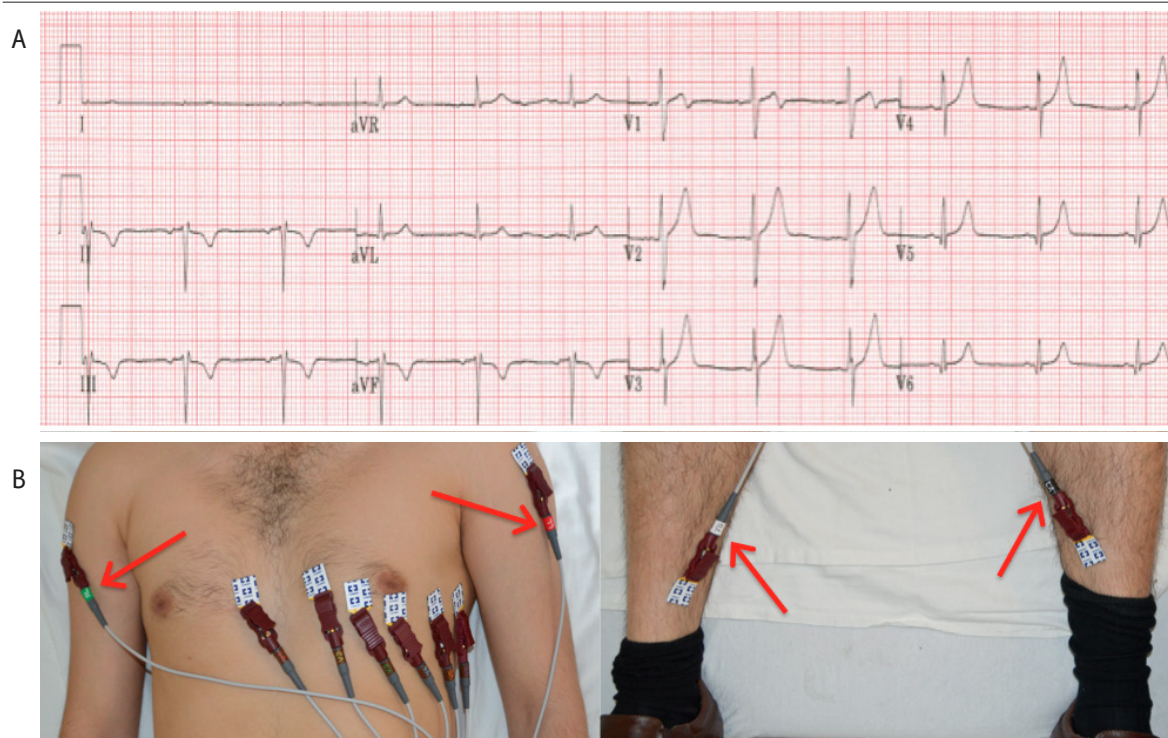




**Figure 7.** 12 lead ECG depicting right arm and left leg reversal. (A) ECG recording. (B) Arrows point to reversal of leads on right arm and left leg.



**Figure 8.** 12 lead ECG depicting dual-lead reversal. (A) ECG recording. (B) Arrows point to reversal of leads on right and left arms and legs.





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## Acknowledgments

None.

## Conflict of Interest Statement & Funding

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

## Author Contributions

Conception and design the work/idea: AR AB. Collect data/obtaining results: AR SK CS. Analysis and interpretation of data: AR SK CS AB. Write the manuscript: AR SK. Critical revision of the manuscript: AR SK AB. Approval of the final version: AB. Contribution of patients or study material: SK CS AB. Administrative or technical advice: CS.

## Cite as:

Rosen AV, Koppikar S, Shaw C, Baranchuk A. Common ECG Lead Placement Errors. Part I: Limb Lead Reversals. *Int J Med Students.* 2014 Jul-Oct;2(3):92-8.

# Common ECG Lead Placement Errors. Part II: Precordial Misplacements

Allison V. Rosen,<sup>1</sup> Sahil Koppikar,<sup>2</sup> Catherine Shaw,<sup>3</sup> Adrian Baranchuk.<sup>3</sup>

## Abstract

**Background:** Electrocardiography is a very useful diagnostic tool. However, errors in placement of ECG leads can create artifacts, mimic pathologies, and hinder proper ECG interpretation. This is the second of a two-part series discussing how to recognize and avoid these errors. **Methods:** 12-lead ECGs were recorded in a single male healthy subject in his mid 20s. Various precordial lead misplacements were compared to ECG recordings from correct lead placement. **Results:** Precordial misplacements caused classical changes in ECG patterns. Techniques of differentiating these ECG patterns from true pathological findings were described. **Conclusion:** As in Part I of this series, recognition and interpretation of common ECG placement errors is critical in providing optimal patient care.

**Keywords:** Cardiology, Electrocardiography, Medical Errors, Precordial Lead Placement, Medical Education (Source: MeSH-NLM).

## Introduction

As discussed in Part I of this series, electrocardiography (ECG) has been established as a useful diagnostic tool.<sup>1,3</sup> Accuracy in ECG recording, whether from trained experts or other medical professionals, is essential in order to reliably interpret medical information.<sup>4</sup> If ECGs are recorded or interpreted by inexperienced individuals, results may be incorrectly interpreted, and patients may be treated according to false information.<sup>5-9</sup> There are characteristic ECG placement errors that can be recognized, and the REVERSE mnemonic can facilitate recognition of placement errors based on abnormal ECG findings.<sup>10</sup>

Electrode misplacements have been shown to occur in as many as 4% of recordings in intensive care units.<sup>2,11</sup> When considering both limb lead reversals and precordial reversals, it is perhaps easy to imagine how limb leads might be mistakenly applied; all are long leads, and left and right sides might be confused on swift application of leads. Contrastingly, precordial leads are bundled together as a group. This explains the low frequency of limb and precordial lead reversals.<sup>12</sup> Precordial errors isolated to the precordial leads are expanded on more in this paper, where we discuss complete reversals of leads V1-V6. Additionally, inaccurate placement of precordial leads poses a significant problem. Leads V1 and V2 can be placed either too high or too low, causing characteristic findings in each case.<sup>13</sup> This type of error involving V1 and V2 occurs in up to 50% of ECG recordings.<sup>14</sup>

The purpose of this study is to review some of the most common recording errors. For the purpose of clarity, this work has been divided into two parts. Part I discussed limb lead reversals.<sup>2</sup> Part II will deal with precordial placement errors.

## Methods

The same subject was analyzed as in Part I of this series, by the same technician and with the same ECG machine (General Electric, Mac 5500, United States) set up at 150 Hz, 25.0 mm/s, and 10.0 mm/V (*Figure 1*).<sup>2</sup> A series of precordial lead misplacements were conducted in order to recreate these classic patterns.

## Results

### V1-V2 in Third Intercostal Space

RSuperior placement of the V1 and V2 electrodes is a common error.<sup>15</sup> The high position of these electrodes causes the R wave amplitude to decrease by approximately 0.1mV in leads V1-V2 along with poor R wave progression across the precordial leads (*Figure 2*).<sup>16-19</sup> Furthermore, the key to detecting a high V1-V2 placement is the absence of a positive P wave in V2, accompanied by a biphasic P wave in V1 with a predominantly negative component. However, the negative P wave in V1 is noted to be more important for discrimination purposes than V2 findings.<sup>5,20</sup>

These findings can mimic an anterior or anteroseptal myocardial infarction, however, a negative P wave in V2 in conjunction with a biphasic P wave in V1 is not common in acute coronary syndromes. Furthermore, misplacement of V1-V2 electrodes can be confirmed by recording normal R wave progression from lower locations on the thorax. If an anterior infarct was the cause of the poor R wave progression, it would persist in the lower leads.<sup>17</sup> The superior placement of V1-V2 electrodes can also potentially mimic Brugada syndrome.<sup>13</sup> Brugada syndrome is a potentially lethal cardiac channelopathy that presents with distinct patterns in the right precordial leads V1, V2, and V3.<sup>21,22</sup> The type 1 pattern has high sloping, coved type ST segments

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Submission: Sep 3, 2014  
Acceptance: Sep 20, 2014  
Process: Peer-reviewed

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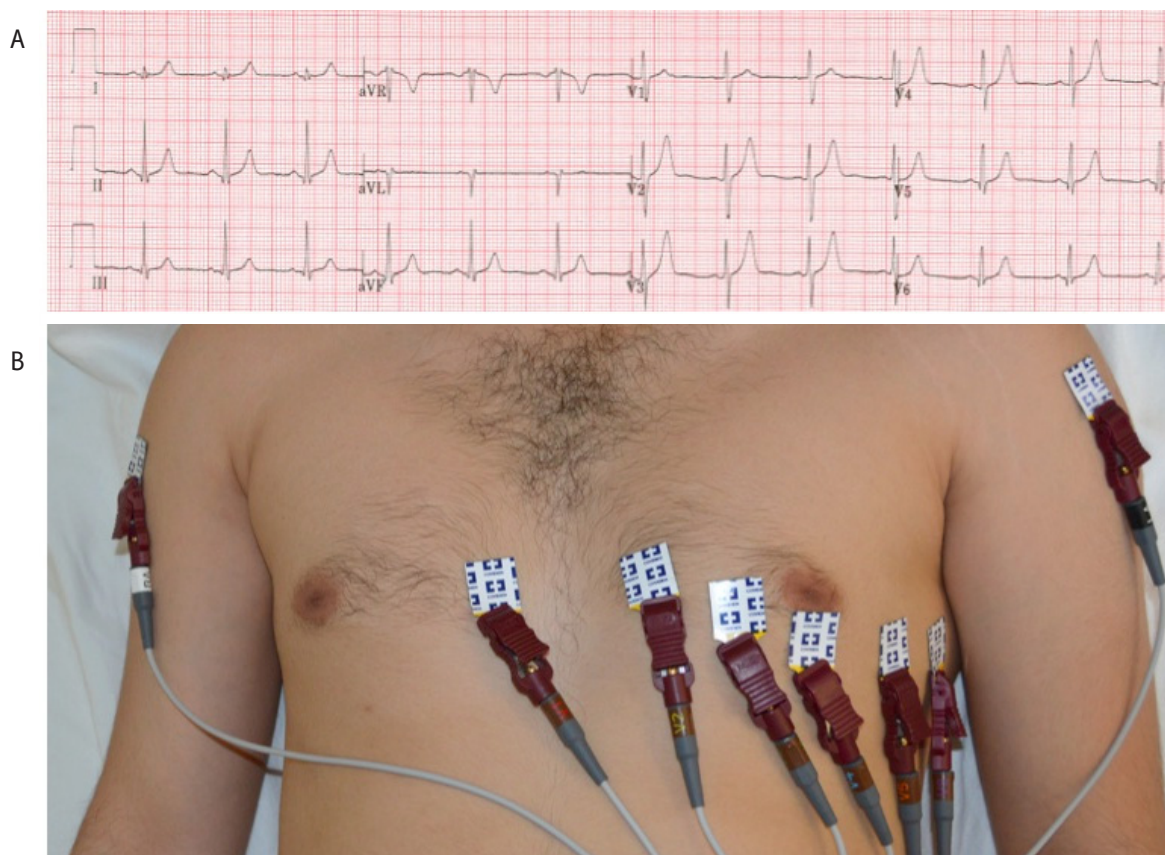
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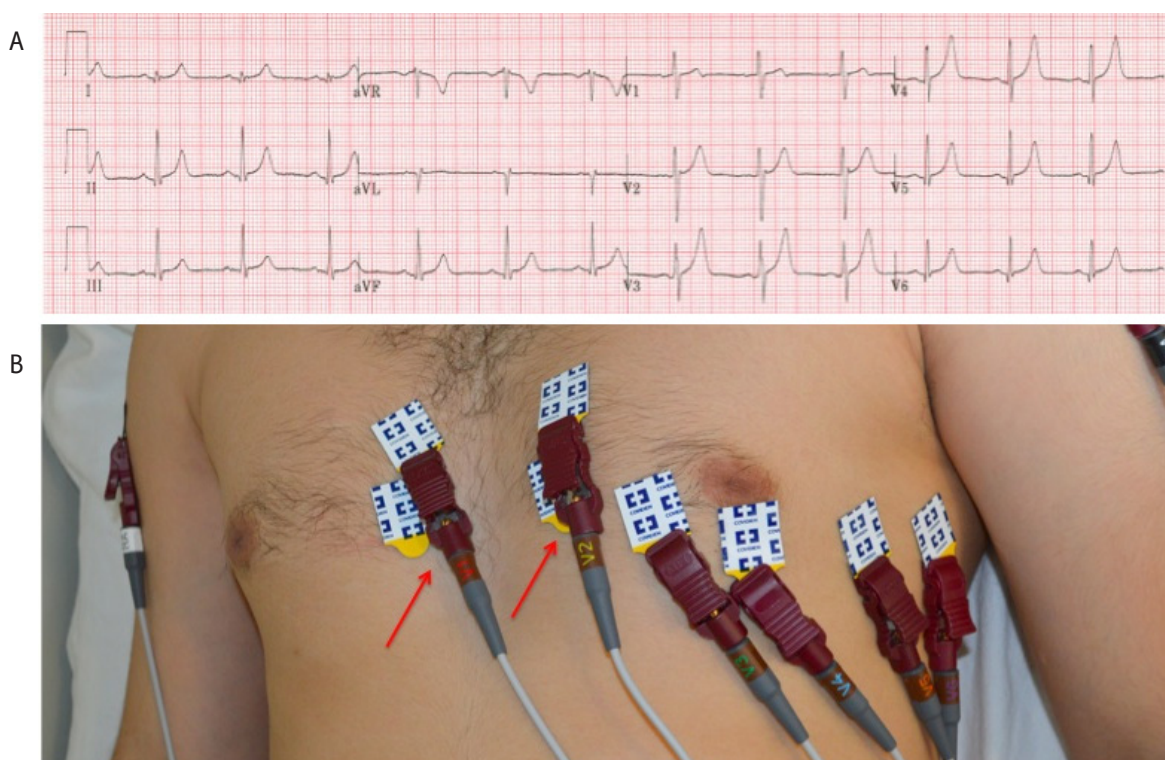
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**Figure 1.** 12 lead ECG depicting correct lead placement. (A) ECG recording. (B) Correct lead placements on chest and arms.



**Figure 2.** 12 lead ECG depicting V1 and V2 placed in the third intercostal space. (A) ECG recording. (B) Arrows point to reversal of leads on precordium.





with negative T-waves. The type 2 pattern has high elevated, saddle back ST segments with variable or flat T-waves in V1 or V2. Brugada syndrome can be mimicked by a number of causes, including improper use of high and low-pass filters, and can be difficult to observe in patients with cardiac abnormalities such as arrhythmias,<sup>23-25</sup> r' waves in leads V1-V2,<sup>26</sup> or pectus excavatum.<sup>27</sup> As Brugada syndrome is potentially lethal, but also easily obscured by filters or other errors, it is important to carefully ensure none of these errors persist if the diagnosis is suspected.<sup>28</sup> Brugada syndrome can be differentiated from electrode misplacement by noting an absence of the clinical criteria required for diagnosis along with a normalization of the ECG upon placing the electrodes on lower locations on the thorax.<sup>29,30</sup>

### V1-V2 in Fifth Intercostal Space

Inferior placement of the V1-V2 electrodes does not produce a significantly altered ECG, and can go unrecognized in many cases (Figure 3). The major change noted is that the low position of these electrodes can cause the R wave amplitude to increase by approximately 0.1mV in leads V1-V2 per inferior interspace.<sup>17</sup>

### V1-V6 Reversal

Exchanging two or more precordial leads is another common error.<sup>31</sup> The major finding in these errors is abnormal progression of the R wave in the affected leads (Figure 4). In a normal ECG, lead V1 shows an rS-type complex, with a steady increase in the size of the R wave and decrease in the S wave amplitude as it moves towards V6. Leads V5 and V6 will predominantly show a qR-type complex. However, in the case of precordial lead reversals, one or more electrodes have a marked deviation from this progression, and this standout area is representative of the misplaced precordial lead or leads.<sup>5,20</sup> In this specific case, the ECG shows an unexpectedly tall R wave in V1 and a deep S wave in V6. As these two leads do not follow the

expected pattern, it should raise the suspicion for a V1-V6 lead reversal.

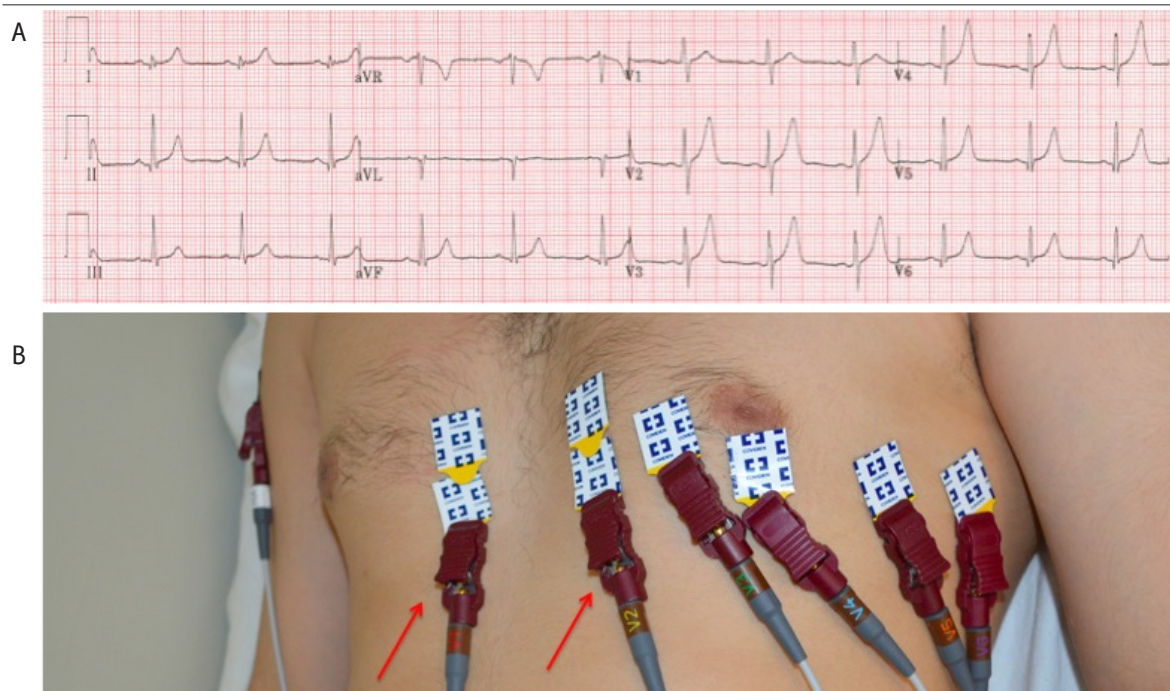
On a quick examination of the ECG, a V1-V6 reversal can be potentially misinterpreted as a right bundle branch block (RBBB).<sup>5</sup> However, a RBBB presents with a M-shaped QRS complex rather than a qR-type complex. Additionally, the lateral leads (I, aVL, V5-V6) may present with a wide, slurred S wave along with ST depression and T wave inversion in V1-V3, neither of which are observed in a V1-V6 reversal. A V1-V6 reversal can also be mistaken for right ventricular hypertrophy (RVH).<sup>5</sup> While RVH has a dominant R wave in V1 and a dominant S wave in V5 or V6, there is also a right axis deviation, which is not observed in a V1-V6 lead reversal.

It is important to note that swapping of precordial leads with limb leads may occur, but is rarely noticed, since the physical bonds between the six precordial leads makes this misplacement difficult.<sup>31</sup>

### V1-V6 Complete Reversal

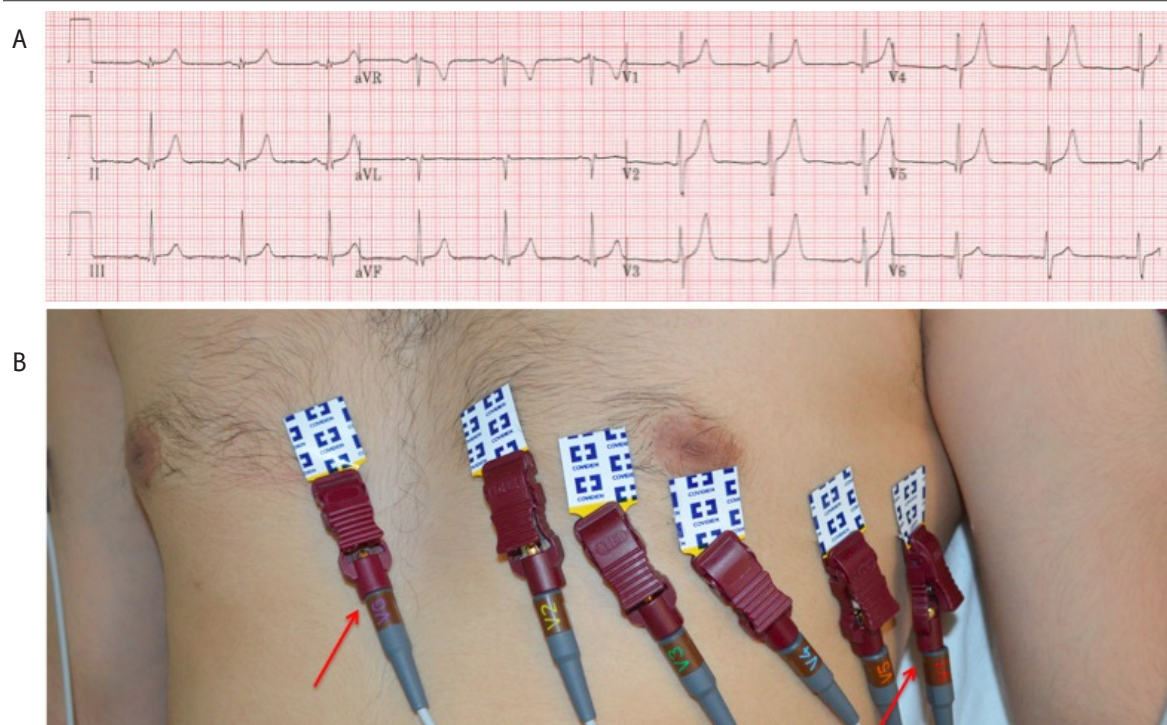
A complete reversal of all the precordial electrodes results in the reversal of the R wave progression. The R wave will decrease its amplitude from V1 to V6 and the S wave will increase its amplitude (Figure 5). This is similar to findings in dextrocardia or a posterolateral myocardial infarction.<sup>31</sup> Dextrocardia would present with inversion of P waves and QRS complexes in leads I and aVL, along with poor R wave progression. Precordial lead reversal can be differentiated from dextrocardia since limb abnormalities would not be found in the case of a reversal.<sup>5,20,31</sup> A posterolateral infarction would present with tall broad R waves in V1-V3, upright T waves and horizontal ST depression. While tall R waves and upright T waves can be seen in the case of a V1-V6 complete reversal, the ST depressions are not present, and can help rule out a posterior infarct.

**Figure 3.** 12 lead ECG depicting V1 and V2 placed in the fifth intercostal space. (A) ECG recording. (B) Arrows point to reversal of leads on precordium.

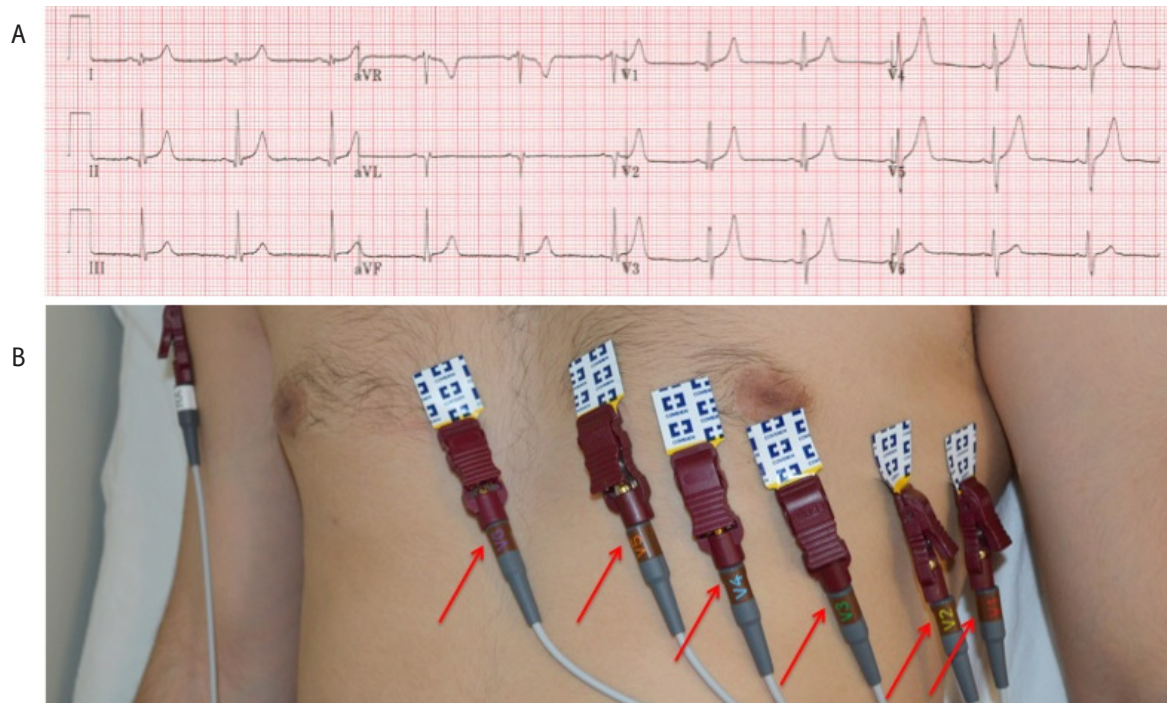




**Figure 4.** 12 lead ECG depicting reversal of V1 and V6. (A) ECG recording. (B) Arrows point to reversal of leads on precordium.



**Figure 5.** 12 lead ECG depicting complete reversal of leads V1-V6. (A) ECG recording. (B) Arrows point to reversal of leads on precordium.



## Discussion

Precordial electrode misplacements can lead to morphological changes on ECG that could potentially be interpreted as pathologic. Common misinterpretations of precordial lead misplacements can be myocardial infarction, genetic channelopathies such as Brugada syndrome, bundle branch blocks or pathologies such as dextrocardia. Electrode misplacements are common in outpatient clinics and intensive care units.<sup>5</sup> Inter-

tingly, incorrect placement of specifically V1 and V2 has been estimated to occur in 50% of ECG recordings.<sup>15</sup> The REVERSE mnemonic is a tool that outlines the most frequent abnormal findings on ECG.<sup>2,5</sup> Of note to our cases, reversal of precordial electrodes V1-V6 is identified in the mnemonic. Careful use of mnemonics such as REVERSE can eliminate errors in ECG recording and interpretation, leading to a reduction in false findings and an increase in diagnostic accuracy.

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## Acknowledgments

None.

## Conflict of Interest Statement & Funding

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

## Author Contributions

Conception and design the work/idea: AR AB. Collect data/obtaining results: AR SK CS. Analysis and interpretation of data: AR SK CS AB. Write the manuscript: AR SK. Critical revision of the manuscript: AR SK AB. Approval of the final version: AB. Contribution of patients or study material: SK CS AB. Administrative or technical advice: CS.

## Cite as:

Rosen AV, Koppikar S, Shaw C, Baranchuk A. Common ECG Lead Placement Errors. Part II: Precordial Misplacements. *Int J Med Students.* 2014 Jul-Oct;2(3):99-103.

# Medical Students' Knowledge and Attitudes Toward Female Sex Workers and Their Occupational Risk Factors

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## Abstract

**Background:** The tendency for female sex workers to seek health care is highly influenced by physician attitudes and behavior. By identifying medical students' attitudes toward female sex workers and assessing their knowledge of barriers to seeking care, we can focus medical training and advocacy efforts to increase access to care and improve public health outcomes. **Methods:** In this cross-sectional study, medical students from various countries were invited to participate in an online survey with close-ended questions and Likert scale statements. Responses were quantified and knowledge and attitude scores were assigned based on knowledge of barriers to seeking care and agreement with positive and negative attitude statements. **Results:** A total of 292 medical students from 56 countries completed the survey, of whom 98.3% agreed that it will be their job to provide treatment to patients regardless of occupation. Self-identified religious students conveyed more negative attitudes toward female sex workers compared to those who did not identify themselves as religious ( $p < 0.001$ ). Students intending to practice in countries where prostitution is legal conveyed more positive attitudes compared to those intending to practice in countries where prostitution is illegal ( $p < 0.001$ ). **Conclusion:** Medical students largely agreed on the importance of providing care to female sex workers as a vulnerable group. In addition to addressing knowledge gaps in medical education, more localized studies are needed to understand the religious and legal influences on attitudes toward female sex workers. Such information can help focus the efforts in both medical education and communication training to achieve the desired behavioral impacts, reconciling the future generations of health care providers with the needs of female sex workers.

**Keywords:** Students, Medical; Attitude of Health Personnel; Sex Workers; Social Determinants of Health; Reproductive Rights (Source: MeSH-NLM).

## Introduction

In 2012, the Scelles Foundation released the first world report on sexual exploitation (Available at: [http://www.fondations-scelles.org/pdf/rapport\\_mondial/sexual\\_exploitation\\_prostitution\\_Fondation\\_Scelles.pdf](http://www.fondations-scelles.org/pdf/rapport_mondial/sexual_exploitation_prostitution_Fondation_Scelles.pdf), updated 2012 January, cited 2014 September 4) and estimated that there are approximately 42 million female sex workers (FSWs) worldwide. This figure is a likely underestimate due to the criminalization and the differing definitions of sex work that render FSWs a difficult-to-reach demographic.<sup>1</sup> Globally, FSWs bear a higher burden of sexually transmitted diseases (STDs) and sexual abuse than do other members of the population.<sup>2-6</sup> A pooled analysis of articles from 2007 to 2011 revealed that in low- and middle-income countries, female sex workers were 13.5 times more likely to be living with human immunodeficiency virus (HIV), compared to other women of reproductive age.<sup>7</sup> Furthermore, sex work is often associated with sex trafficking and decreased negotiating power over the terms of sex, permitting elements of physical and emotional violence that exacerbate morbidity.<sup>2-6</sup>

A complex interplay of social, political, economic and structural obstacles serve as barriers to seeking health care for FSWs. These include social stigma, fear of criminal persecution, lack of autonomy over health-related decisions and negative experiences within the health system.<sup>8-13</sup> From the public health perspective, ensuring protective mechanisms for sex workers

is not only an issue of human rights for vulnerable individuals, but also of controlling routes of STD transmission within the general population.<sup>3,14</sup> Indeed, the International AIDS Society reported that an estimated 15% of HIV infections in the general adult female population could be attributed to unsafe female sex work (Available at: [http://www.iasociety.org/Web/WebContent/File/KAPs\\_Fact\\_Sheet\\_Sex\\_Workers.pdf](http://www.iasociety.org/Web/WebContent/File/KAPs_Fact_Sheet_Sex_Workers.pdf), updated 2014 March, cited 2014 September 4).

Health care providers themselves have a significant role in ensuring health rights for their patients, potentially advocating for the provision of care to sex workers as a vulnerable population.<sup>15-17</sup> Negative experiences with doctors—anxiety associated with physical exams, discomfort with discussing sensitive topics such as STDs, fear of judgment by medical professionals or male doctor insensitivity to female sex workers' needs—can become significant barriers to service use.<sup>4,10,18-21</sup> These findings highlight the importance of health care provider attitudes and behavior in shaping the patient experience and, ultimately, health outcomes.

Despite the proven influence of health care providers on the utilization of care, there has been little research assessing the competence of medical students in their ability to provide for those involved with sex work. With the aim to produce competent future doctors, medical institutions have the responsibility of training students to identify socio-economic risk factors for

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Submission: Jul 28, 2014  
Acceptance: Sep 13, 2014  
Process: Peer-reviewed

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disease, promote access to care and provide specialized care to vulnerable individuals. For that reason, knowledge and attitudes of medical students toward FSWs need to be assessed to identify any misconceptions or attitudes that may compromise care for this particular group of patients in the future. With proper training, medical students may help improve health outcomes by reducing barriers to seeking care.

The aim of this study was to identify medical students' attitudes toward female sex workers and knowledge of risk factors, such as potential barriers to seeking care, associated with the sex industry. The results would identify gaps in knowledge, attitudes and practices and underscore any common misconceptions and factors leading to negative attitudes or unwillingness to provide care. These results could be used to target specific attitudes or areas of doubt, direct the integration of social and occupational determinants of health within medical training and enable the future generations of doctors to be well-prepared advocates for FSW health and the health of the general population.

## Methods

This cross-sectional study collected data for a five-month period from August 2012 to January 2013. Participation was invited through the International Federation of Medical Students' Associations (IFMSA), which is a non-governmental, international body that encompasses 108 medical student organizations across 101 different countries. The IFMSA is an appropriate source for international representation of medical students, since the web-based, transnational communication among members is frequent and reliable.

Using the IFMSA email server, all medical student members of the IFMSA were invited to participate in a web-based survey on medical student attitudes toward sex workers and knowledge of occupational risk factors associated with this specific group of patients. The target population included all English-speaking IFMSA members currently enrolled in medical programs at the time of data collection. The emailed invitation letter included a link to an online survey created through SurveyMonkey.com LLC. By proceeding to the online survey, students confirmed their informed consent to participate in the study.

Knowledge and attitudes were quantified using scales similar to those used in the study of health care providers' attitudes toward sex workers by Phrasisombath, et al.<sup>20</sup> Based on their answers to multiple-choice questions included in the survey, participants received a total knowledge score that was assessed as a raw score. To account for uncertainty and omissions, this score was also assessed as a percentage of total questions answered. Knowledge questions were based on data from previous studies on FSW health risks and care-seeking behavior.<sup>2-6,8-13,20-22</sup> The legality of prostitution in specific countries was based on the Joint United Nations Programme on HIV/AIDS (UNAIDS) data from 2010 in an online information sheet ([http://www.unaids.org/en/media/unaids/contentassets/documents/priorities/20100728\\_HR\\_Poster\\_en.pdf](http://www.unaids.org/en/media/unaids/contentassets/documents/priorities/20100728_HR_Poster_en.pdf)).

Attitudes were quantified based on a scale of 1-5, with "1" corresponding to "strongly disagree" and "5" to "strongly agree" for positive attitude statements. The scale was reversed for negative attitude statements. Therefore, agreement with more positive atti-

des would overall approach a "5" score for each question, yielding a total score of 45 for the greatest agreement with positive attitude statements. With a maximum score of 45, a score greater than or equal to 22 was interpreted as an overall "positive attitude," and a score less than 22 was interpreted as an overall "negative attitude."

Data was analyzed using StatPlus® (2009) and Microsoft Excel® (2011). Descriptive statistics were generated to survey attitudes toward female sex workers and assess general knowledge of potential barriers to seeking care. Linear regression was conducted to determine whether there was any correlation between knowledge and attitude scores. Regression analysis was also conducted to find any correlation between years of experience, measured by age and number of terms in medical school, and student knowledge or attitudes.

Two-sample T-tests were conducted to determine the significance of any differences in attitudes and knowledge found among the groups of students identified upon observational analysis as having disparate answers, i.e. those groups divided by sex, religiousness, legality of prostitution in country of intended practice and prior education in social determinants of health and/or occupational health. For these comparisons, knowledge was measured both by a difference in mean knowledge scores and a difference in the percentage of correctly answered knowledge questions. Attitudes were measured by a difference in mean attitude scores. For all T-tests, a significant difference was accepted if the corresponding p-value fell below 0.05.

Institutional Review Board approval to ensure the ethical nature of this investigation was obtained through St. George's University (Reference No. 12024).

## Results

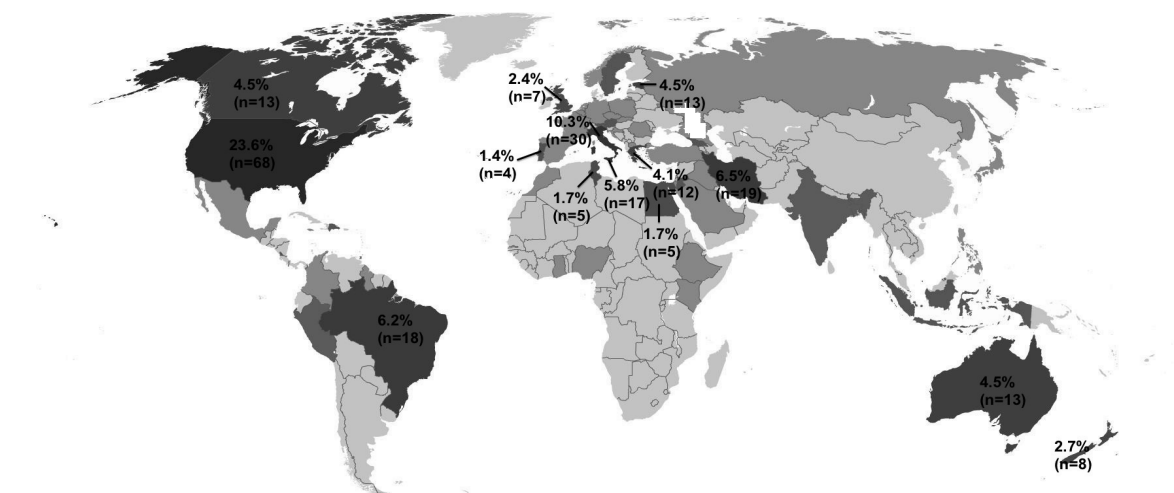
### Demographics

A total of 292 medical students from 56 countries completed the survey (participation rate=75.1%). Countries that were most represented included: the United States (n=68), Italy (n=30), and Iran (n=19) (*Figure 1*). Of all participating students, the median age was 23 years old, with the median medical school experience equaling six terms (three years) and a slight majority being female (57.2%, n=167).

### Knowledge responses

Regarding knowledge of FSW vulnerability and barriers to seeking care, students completed an average of 15 out of 20 questions, marking the answers to 5 out of 20 questions as "uncertain." Of those questions which were completed, an average of 92% were answered correctly. For example, large majorities demonstrated the understanding that FSWs are at increased risk for morbidity associated with sexually-transmitted infections (89.4%, n=261), violence (85.3%, n=249), and drug abuse (78.7%, n=230). The majority of the students were also aware that certain factors, such as health care provider perceptions (90.8%, n=265), financial burden (90.4%, n=264) and comfort with knowing test results (91.7%, n=268), are important factors in FSW decisions to seek care. With regards to knowledge about policy, 16.2% (n=45) were uncertain whether prostitution is legal in the country where they intend to practice medicine, and 27.4% (n=76) incorrectly reported that prostitution is either legal or illegal when the opposite is true. Numbers of correct responses did not vary significantly



**Figure 1.** Percentages of participants from the top 14 most represented countries\*

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

by sex, educational background, self-identified “religiousness”, country of origin or country of intended practice.

#### Attitude statements

Of all students, 96.5% (n=277) received a summary attitude score reflecting a positive attitude. There were large percentages of agreement with two positive-attitude statements: 98.3% (n=297) of students either agreed or strongly agreed that it will be their job to provide treatment to patients regardless of occupation and 81.9% (n=239) either agreed or strongly agreed that FSWs comprise a vulnerable population that deserves particular attention. There was a prevailing agreement (68.4%, n=199) with one negative-attitude statement in particular, that FSWs who do not seek care when necessary are irresponsible.

Large percentages of students were uncertain whether they agreed or disagreed with the following attitude statements: that FSWs tell the truth about symptoms of sexually transmitted infections (51.7%, n=150), FSWs follow treatment for symptoms of sexually transmitted infections (63.9%, n=186) and that students themselves, as future doctors, will have enough time with their patients to identify victims of violence or human trafficking (39.9%, n=116).

Upon further analysis of the data by participant demographics, we found significant differences in mean attitude scores when students were divided by two criteria in particular: self-identified religiousness and the legality of prostitution in the country of intended practice. Self-identified religious students conveyed more negative attitudes compared to those who did not identify themselves as religious ( $p<0.001$ ) and students intending to practice where prostitution is legal conveyed more positive attitudes compared to those intending to practice where prostitution is illegal ( $p<0.001$ ). Groups analyzed based on other variables, such as sex and prior education in social determinants of health and/or occupational health, showed no significant variation in attitudes.

#### Relationship between knowledge and attitudes

With regression analysis of knowledge and attitudes, we found that knowledge was positively correlated with attitudes, with higher knowledge scores of FSW risk factors and barriers to seeking care corresponding to higher (more positive) attitude scores

( $r=0.163$ ,  $p=0.006$ ). There was no correlation between years of experience, measured both by age and by number of terms in medical school, and knowledge scores. In addition, there was no correlation between years of experience and attitude scores.

## Discussion

Medical students from different backgrounds largely agreed on the importance of providing care to FSWs as a vulnerable group. The near-unanimous agreement across different countries, cultures, and political environments reflects the potential for the medical profession to be a nonpartisan, secular space in which patient welfare and human rights take precedent over physician biases. This support for human rights can be leveraged to strengthen equitable medical practice, focusing training and advocacy on the areas of doubt that may influence access to and quality of services. Nonetheless, the results of this study present medical education with significant challenges. In order to address gaps in education and training, we may need to focus education outside of medical institutions to include religious and political sectors that may influence medical student attitudes. Therefore, we will first explore how specific medical student competencies might be improved through formal education, followed by how concerted efforts toward health equity might be achieved through partnerships between medical education and other sectors of society.

The first area of doubt to address is the marked uncertainty regarding FSW truthfulness about symptoms and compliance with medications. While this uncertainty most likely reflects a lack of experience working with such population, it would be problematic if future treatment becomes based on assumptions about honesty and compliance rather than respectful consideration of unique patient needs. Previous studies on FSWs have shown that others' negative perceptions, including those of health care providers, are among the most important factors in influencing a FSW's decision to seek care.<sup>4,10,18-21</sup> According to UNAIDS and other advocacy group publications, sensitivity training for medical students and physicians that emphasizes individual patient concerns and capabilities may ensure more feasible treatment options and increase the likelihood that FSW patients will return for care (Available from: <http://data.unaids.org>).

[org/publications/IRC-pubos/jc438-femsexwork\\_en.pdf](http://org/publications/IRC-pubos/jc438-femsexwork_en.pdf), updated 2000 November; cited 2014 May 29).<sup>22</sup>

Secondly, the prevailing agreement that “FSWs who do not seek care when necessary are irresponsible” implies medical students’ lack of awareness of multiple barriers to seeking care. Underlying this attitude is the misconception that FSWs are autonomous and can therefore seek help at will, when in fact there are many structurally-reinforced obstacles to seeking medical attention. These include the inability to leave work premises, dependence on employers for health information, financial instability and fear of criminal persecution.<sup>8-13,21</sup> The finding that many students did not understand the legal environment of prostitution in their countries of intended practice is not surprising, considering the complex nature of legislature regarding sex work. Nonetheless, the assumption of FSW responsibility in the context of such obstacles reiterates the need for medical students to understand barriers to seeking care in order to best encourage access. While many of the obstacles exist within the term of “sex work” itself, professionals can encourage health-care seeking behavior by reassuring confidentiality and safety measures within the health care system and referring to protection programs when necessary.<sup>16</sup>

Finally, efforts must be made to address the large percentage of students who doubted they would have enough time to identify victims of violence. Such identification may not require additional time than that of a thorough history and physical exam.<sup>4</sup> Therefore, medical institutions should continue to emphasize risk factors and warning signs associated with sex work and sex trafficking to increase the awareness of health care professionals of the at-risk individuals who may present within their patient population.<sup>4,5</sup>

The aforementioned educational targets (dispelling prejudices to encourage patient-centered care, adequate education about obstacles to seeking care and adequate training in recognizing warning signs of abuse associated with sex work) are only preliminary components of a concerted effort to sensitize medical students to the role of physicians in promoting the health of sex workers. In the World Health Organization’s Communication for Behavioral Impact (COMBI) toolkit, authors state that “Experts have come to realize that community understanding of diseases and their spread is complex, context-dependent and culturally mediated. Integration of participatory approaches in public health responses is essential to look in the right places, ask the right questions and listen more effectively before making technical recommendations and implementing interventions” (Available at: [http://www.who.int/ihr/publications/combi\\_toolkit\\_outbreaks/en](http://www.who.int/ihr/publications/combi_toolkit_outbreaks/en), updated 2012; cited 2014 May 30). Participatory approaches take into consideration the factors that influence attitudes and the matters that are deeply important to individuals in order to find feasible, mutually beneficial, sustainable behaviors.<sup>24</sup> Medical students and physicians may deeply value acknowledgment of patient needs, adherence to personal moral values and/or promotion of social justice, all in variable orders of priority.<sup>25-27</sup> COMBI action plans, historically successful for vector-borne disease prevention (Available at: [http://www.tropika.net/review/061001-Dengue\\_Behaviour\\_change/article.pdf](http://www.tropika.net/review/061001-Dengue_Behaviour_change/article.pdf), updated 2006; cited 2014 May 30), are also applicable for other family and community health initiatives and may improve sexual and reproductive health outcomes by reconciling health care provider interests with the health needs of female sex workers.<sup>28</sup>

Our results suggested that student attitudes were polarized mostly by personal moral beliefs (self-identified religiousness) and the legal environment (legality of prostitution in the country of intended medical practice), rather than by other variables such as age, number of years in medical school and previous education in social determinants of health or occupational health. It would be beneficial for future studies to investigate how personal moral beliefs and political environments may influence attitudes, compared to experience within the medical education system. Due to personal moral beliefs and legal environments varying significantly among societies and cultures, medical students would need to be surveyed on more local yet comprehensive scales in order to appreciate the role of specific religions on professional attitudes and legal restrictions on medical practice, medical student and physician priorities when addressing FSWs and the socioeconomic nuances that shape resource availability. Understanding these influences is the first step in developing regional COMBI action plans, leveraging medical students’ desire to provide services that fit within their moral and political frameworks, while ensuring access to attentive, quality health services for FSWs.

Limitations of this study include a relatively small sample size and participation bias, with students who voluntarily participated more likely to be enthusiastic about issues of health equity. IFMSA is embedded in global health activism, so members of the IFMSA are more likely to select answers with a consciousness toward human rights. Data were also influenced by the most-represented countries’ cultural perceptions of prostitution, the role of the health care professional, and rights toward reproductive health decisions, among many factors influencing attitudes. Female participation was slightly higher; however, we believe this is not a strong limitation to our study since there is no significant statistical difference in responses between males and females. For these reasons, we cannot make generalizations about the world’s population of medical students. However, our results may lay a basis for future studies to investigate how religious backgrounds and surrounding policy for sex work might influence medical student knowledge, attitudes and practice toward female sex workers and, therefore, local health outcomes.

Medical students from different backgrounds largely agreed on the importance of providing care to female sex workers as a vulnerable group. However, students expressed marked uncertainty regarding FSW truthfulness and compliance as patients, demonstrated low level of awareness to FSW barriers to seeking care and uncertainty of their own competency as future health care providers. Together, these may negatively impact the quality of care. While formal training in FSW vulnerabilities and needs are a first step toward building health care personnel competencies, this study suggested that students may be more influenced by religious notions and local legislation toward sex work than education. Therefore, further studies are needed to understand the sociocultural and political influences that shape the provision of health care so that focused “communication for behavioral impact” programs can be implemented. With appeal to the widespread and non-discriminatory agreement to serve vulnerable populations, such efforts must bring access to care for FSWs to the forefront of medical-based human rights issues, empowering health care professionals to promote quality, nondiscriminatory, patient-centered care as an inalienable human right. These efforts are particularly fundamental for those at risk and necessary for improved public health in our communities.

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## Acknowledgments

The authors would like to thank Mr. Michael Gann for his help in data analysis; the International Federation of Medical Students' Associations and all participating students for their contributions to this study.

## Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose. The primary investigator independently provided all financing for this study.

## Author Contributions

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

## Cite as:

Nakagawa JT, Akpinar-Elci M. Medical Students' Knowledge and Attitudes Toward Female Sex Workers and Their Occupational Risk Factors. *Int J Med Students.* 2014 Jul-Oct;2(3):104-8.



# Penile Cancer in Cali, Colombia: 10 Years of Casuistry in a Tertiary Referral Center of a Middle-Income Country

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## Abstract

**Background:** Background: Penile cancer is a rare disease in Colombia; in Cali, it represents 0.7% of all cancers. Penile cancer has been associated with old age, bad hygiene, smoking and lack of circumcision. This study aimed to describe the sociodemographic and clinical characteristics of patients with penile cancer who consulted to a tertiary referral hospital. **Methods:** A case series of all penile cancer cases at a reference institution in Cali during 2001-2010. Socioeconomic, demographic and clinical features of patients were described, and bivariate analyses were carried out. **Results:** There were 46 penile cancer cases. The average age was  $60 \pm 16.9$  years. The main reason for consultation was an exophytic mass on the penis (75.0%). The most common location was the glans (69.6%), and the more frequent histology type was the squamous cell carcinoma (95.7%). With regard to risk factors, 65.5% of the patients had history of smoking and 90.9% did not have circumcision. Patients who underwent radical amputation had higher rates of positive nodes (55% vs. 13.5%,  $p=0.015$ ) and ulcerative lesions (77.8% vs. 29.7%,  $p=0.018$ ) than those who did not have the procedure done. Recurrence was associated with the presence of lymphadenopathy ( $p=0.02$ ) and history of circumcision ( $p=0.015$ ). **Conclusion:** Most of the patients with penile cancer found in this study had old age, history of tobacco use and lack of circumcision. Patients who presented with lymph node metastasis had to undergo more radical procedures and suffered a greater rate of recurrence compared with those without lymph node involvement. Robust studies to determine the risk factors among low-income populations are required.

**Keywords:** Penile Neoplasms; Circumcision, Male; Smoking; Developing Countries (Source: MeSH-NLM).

## Introduction

Penile cancer is a rare malignancy worldwide, accounting for less than 0.5% of all cancers diagnosed in men.<sup>1</sup> It is less common in high-income countries like Europe and the United States, where it accounts for 0.4%-0.6% of all malignancies, with an age-adjusted incidence of 0.3 to 1 in 100,000 men.<sup>2,3</sup> In low- and middle-income countries such as African and South American countries, it represents about 10% of all malignancies, with an annual age-adjusted rate between 2.3 to 8.3 per 100,000 men and Brazil being the country with the highest incidence in the world.<sup>4,5</sup>

Penile cancer usually affects men over 50 years, but up to 19% of the cases occur in men under 40 years and 7% in men younger than 30 years.<sup>5</sup> In 95% of the cases, penile cancer originates from the squamous cell tissue located in the inner layer of the glans (80%) or foreskin (15%).<sup>6-11</sup> Risk factors that have been associated with penile cancer include poor hygiene, phimosis, dermatitis, traumatic injury of the penis, infection with the Human Papilloma Virus (HPV) and smoking.<sup>12-14</sup> Early circumcision acts as a protective factor since it prevents phimosis.<sup>15,16</sup>

In 2003, Ramírez and Bermúdez-Pupo published a study describing the population with penile cancer in a referral hospital in Cali, Colombia between 1990 and 2000, in which they found a total of 59 cases of penile cancer, with a mean age of 52 years, 87% of patients had a history of smoking, 10% had HPV

infection and 80% had no circumcision.<sup>17</sup> According to later data from the Population-based Cancer Registry of Cali (RPCC), 63 cases of penile carcinoma were reported during the 2004-2008 period. This type of carcinoma accounted for 0.7% of all diagnosed cancers, and the age-adjusted incidence was 1.3 per 100,000 person-year (Available from: <http://rpcc.univalle.edu.co/in/>, updated 2008; cited 2013 Jun 1).

Although penile cancer is a rare disease in Cali, it can yield terrible consequences on the social and emotional life of patients living with it. The cancer usually afflicts men of low socioeconomic status, and the diagnosis is frequently made in advanced stages of the disease when treatment options are drastic. It is therefore necessary to know the changes in these sociodemographic factors and the clinical features associated with the onset and the prognosis of penile cancer in this population in order to identify research areas and potential prevention strategies. The objective of this study is to describe the sociodemographic and clinical characteristics of patients with penile cancer who consulted to a tertiary referral hospital in Cali, Colombia during 2001-2010.

## Methods

This is a case series study of patients admitted to a public reference institution in Cali with histopathological diagnosis of penile cancer made between January of 2001 and December of 2010. The institution where the study was carried out admits

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Submission: Jun 16, 2014  
Acceptance: Sep 1, 2014  
Process: Peer-reviewed

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patients from the entire southwestern region of Colombia and is one of the most important public institutions in the country. The clinical records of patients registered with the diagnosis of penile cancer were reviewed. For cancer staging, the international TNM classification was used.

The data collection consisted of three parts: sociodemographic characteristics, patient's clinical features and the tumor's characteristics. The database was created in Microsoft Access 2010® program, and an exploratory analysis was performed to look for extreme and missing values, and typing errors.

Some variables were recategorized. Residency was further divided into three groups: Cali, other municipalities of Valle del Cauca and other departments of Colombia. Marital status was divided into two groups: with partner and without partner; occupational status into five groups: unemployed, farmer, various trades, street seller and others; and associated symptoms into six groups: none, urinary, pain, hydrocele, secretion and constitutional.

Univariate and bivariate analyses were performed. Description of the variables was presented using measures of central tendency and dispersion (average and standard deviation [SD]) for quantitative variables and frequencies and percentages for categorical variables. Then, application of hypothesis testing was carried out according to the nature of the variables. For quantitative variables, Student t test was used given the number of groups, the normal distribution and equal variances of the variables analyzed. For categorical variables, Fisher's exact test was used. All analyses were performed with a significance level of 0.05 with Stata13® (StataCorp, TX, USA).

This study is adherent to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Statement.<sup>18</sup> Additionally, it has the approval of the Institutional Review Board of Universidad del Valle.

## Results

### Description of the Study Population

The initial database consisted of 71 clinical histories, of which 25 had to be excluded: 10 had a diagnosis other than penile cancer, 4 were not found in the files, 3 had no confirmed diagnosis, 1 due to illegible handwriting and 7 with a diagnosis date before January 2001. After the exclusions, a total of 46 medical records were analyzed.

The age range was between 29 and 103 years, with a mean age of  $60 \pm 16.9$  years. Two patients (4.3%) were younger than 40 years, and eight patients (17.4%) died during the study period.

Most of the patients (54.3%) had their educational attainment recorded in their medical record. Of these, 60.0% completed basic primary education and one patient (4.0%) had a post-graduate degree. For insurance status, 87.0% of the patients were under the state-subsidized regime, 6.5% did not have any insurance and 4.4% were in the contributory regime.

Most of the patients (78.3%) were from Cali or other municipalities of Valle del Cauca, and the remaining 21.7% were from other departments in the southwest region of Colombia.

In terms of occupation, 37.0% of the patients were farmers and 19.6% were unemployed at the time of the study. Within the group of patients who had an occupation, 59% did their work outdoors in the fields of agriculture, street vending, construction, etc. Finally, for marital status, 54.5% of the patients had a stable partner and 45.5% had no partner.

### Clinical Features

The most frequent cause of consultation among patients studied was the appearance of a mass on the patient's penis (60.9%), followed by the appearance of an ulcer (39.1%). More than two thirds (78.3%) of the patients did not report the presence of adenopathy during the first visit, and 6.5% consulted due to phimosis.

For the physical examination item, 75.0% of the patients had an exophytic mass and 25.0% an ulcer. For tumor localization, 69.6% had the glans involved, 41.3% the penile shaft, 39% the foreskin and 21.7% the coronal sulcus. Involvement of more than one region of the penis was reported in 27.5% of the patients.

Almost half of the patients (45.7%) reported consultation to a general physician or specialist before the diagnosis of penile cancer was made, and 78.6% reported an evolution time between 2 and 24 months. More than half of the patients (58.7%) did not have any additional symptom associated with the cause of consultation. Among those who consulted with additional symptom(s), 17.4% reported urinary symptoms and 13.0% bloody or purulent discharge from the penis.

History of smoking was found in 65.5% of the patients, and 90.9% of the patients had no history of circumcision at the time of their first consultation. The recurrence rate among patients who had had circumcision (2 patients) was 100%, in contrast to the uncircumcised group of patients (27 patients) whose recurrence rate was 8% ( $p=0.015$ ).

History of sexually transmitted diseases (STDs) was denied by 86.7% of the patients; 6.5% of the patients reported a history of syphilis, 4.4% gonorrhea, and 2.2% had human immunodeficiency virus (HIV) infection. The patients with a history of STDs were younger compared with those without such history, with a mean age of  $47.2 \pm 5.38$  years and  $61.8 \pm 17.26$  years, respectively ( $p=0.047$ ). Patients with a history of STD presented with an ulcerative lesion more frequently than patients with no history of STD (66.7% vs. 17.6%, respectively;  $p=0.038$ ) (Table 1).

### Tumor Features

Half of the cases had an advanced T2 or T3 clinical stage. In 37% of the cases, it was not possible to determine the node involvement (NX). Involvement of multiple superficial inguinal nodes (N2) was found in 21.7% of the patients; 19.6% were classified as N1 and 15.2% had no evidence of lymph node metastasis (No). Evidence of metastasis to distant organs was absent (Mo) or could not be determined (MX) in 84.8% of the patients. Patients with nodal involvement (N1-N3) presented metastasis more frequently than those with no evidence of nodal involvement (No, NX): 27% vs. 4%, respectively ( $p=0.042$ ).

Regarding the tumor grade, 65.2% of the cases were well diffe-

**Table 1.** Relationship between Past Medical History and Sociodemographic and Clinical Characteristics of Patients with Penile Cancer Diagnosis in a Tertiary Referral Hospital in Cali, Colombia, 2001-2010.

Characteristic	Smoking				History of STDs				History of Circumcision			
	No	Yes	Total	p*	No	Yes	Total	p*	No	Yes	Total	p*
<b>Education</b>												
None	0	1	1	0.88	3	0	3	0.34	2	0	2	0.63
Basic primary school	5	7	12		11	4	15		11	1	12	
High school	0	2	2		5	1	6		3	1	4	
Postgraduate degree	0	1	1		1	0	1		1	0	1	
<b>Marital status</b>												
Stable partner	6	9	15	1.00	20	4	24	0.43	14	2	16	0.50
No partner	4	8	12		18	2	20		15	1	16	
<b>Form of presentation</b>												
Exophytic mass	9	13	22	0.26	28	2	30	0.04	21	2	23	0.11
Ulcer	0	4	4		6	4	10		7	1	8	
<b>Tumor localization</b>												
Foreskin	6	7	13	0.27	15	3	18	0.44	13	3	16	0.10
Glans	8	14	22	0.54	29	3	32	0.25	23	3	26	0.48
Coronal sulcus	8	2	10	0.01	9	1	10	0.61	7	1	8	0.58
Penile shaft	3	9	12	0.30	16	3	19	0.48	11	0	11	0.28
<b>Histologic Grade</b>												
High grade	0	1	1	0.83	1	0	1	0.83	19	3	22	0.66
Well differentiated	7	12	19		26	4	30		1	0	1	
Undifferentiated	0	1	1		2	0	2		1	0	1	
Moderately differentiated	2	5	7		9	21	11		8	0	8	
<b>Treatment</b>												
Partial amputation	6	12	4	0.57	25	3	28	0.44	20	2	22	0.72
Radical amputation	1	3	18	0.60	7	2	9	0.33	5	1	6	0.46

\* Fisher exact test. STDs: sexually transmitted diseases.

rentiated and 23.9% were moderately differentiated. The predominant histological type was squamous cell carcinoma (95.7%); melanoma was found in one patient (2.2%) and leiomyosarcoma in another patient.

As for the treatment, 60.9% of the patients underwent partial amputation and 20.0% radical amputation. Of these patients, 65.2% also underwent lymph node dissection. Therapeutic alternatives received included chemotherapy (6.5%), radiotherapy (4.5%) and circumcision (10.9%).

None of the 39 patients without evidence of distant metastases and classified as Mo/MX underwent pharmacological management, while 28.6% of the patients classified as M1 received such management ( $p=0.002$ ) (Table 2). The patients who underwent radical amputation had positive nodes and ulcerative lesions at higher rates than those who did not undergo this procedure (positive nodes: 55.0% and 13.5%, respectively,  $p=0.015$ ; ulcerative lesions: 77.8% and 29.7%, respectively,  $p=0.018$ ).

Recurrence was found in 5.8% of the patients; of these, 33.2% involved the stump area. Recurrence was associated with the presence of lymphadenopathy ( $p=0.02$ ) and history of circumcision ( $p=0.015$ ).

## Discussion

The present study allowed for a description of the sociodemo-

graphic and clinical characteristics of patients diagnosed with penile cancer who consulted to a tertiary-level referral institution in Cali over a period of 10 years (2001-2010).

### Sociodemographic Characteristics

It was found that the age groups most commonly affected by this type of cancer were men between 43 and 77 years, similar to results of previous studies that reported a higher incidence in men above 50 years old.<sup>5,19</sup> Chaux et al. reported that up to 91% of patients with penile cancer have a low educational level.<sup>19</sup> This finding is supported by the present study where most patients had completed only basic primary education.

Subscription to a subsidized health insurance regime in Colombia indicates a low-income status. Eight-seven percent of the studied patients belonged to this regime, which is consistent with the study by Hernandez et al. which found a 43% greater risk of penile cancer in countries where more than 20% of the population lives in poverty compared to countries with less than 10% living in poverty.<sup>20</sup> However, it is important to note that the institution where the study was carried out serves primarily the poor population, and this may lead to an overrepresentation of the poor population in the socioeconomic characteristics analysis.

There were no significant differences between the group with stable couples and the unmarried or widowed group, which differ from the scientific literature that suggests a lower frequen-



**Table 2.** Relationship between Clinical Variables and Outcomes in Patients with Penile Cancer Diagnosis in a Tertiary Referral Hospital in Cali, Colombia, 2001-2010.

Characteristic	Smoking			History of STDs			History of Circumcision		
	No	Yes	p	No	Yes	p	No	Yes	p
<b>Past medical history</b>									
Circumcision	3	0	0.74	2	1	0.46	0	2	0.02
Smoking	15	4	0.67	16	3	0.57	14	2	0.72
STDs	39	7	0.51	37	9	0.20	32	6	0.53
<b>Form of presentation</b>									
Exophytic mass	23	5	0.69	22	6	0.50	21	3	0.38
Ulcerative lesion	13	5	0.10	11	7	0.01	12	3	0.44
<b>Treatment</b>									
Pharmacological	0	2	0.02	2	0	0.64	1	0	0.84
Nodal involvement N1-N3	16	6	0.04	16	6	0.53	15	4	0.02

STDs: sexually transmitted diseases.

cy of penile cancer in unmarried men compared with married men (15% and 85%, respectively).<sup>17</sup> The presence or absence of a steady partner as a risk factor is a subject of controversy. A possible association between cervical cancer and penile cancer has been proposed, since flat penile lesions have been found on 60% of the men who are partners of women with cervical intraepithelial neoplasia (CIN).<sup>21</sup> Contrarily, when the presence of premalignant cervical lesions in female partners of men with penile cancer has been studied, the results have not shown a different risk in these women than in the general population.<sup>22</sup>

Ramirez et al. found that the majority of patients with penile cancer were farmers (49.2%), similarly to what was found in this study with 37% of the patients being farmers.<sup>17</sup> Scientific literature reports that farmers are at higher risk for some neoplasms, such as Hodgkin's lymphoma, multiple myeloma, leukemia, melanomas, and cancers of the lip, stomach, and prostate. However, the association between farmer-related occupation and the development of penile cancer has not yet been established. Literature states that chronic exposure to chemicals commonly encountered in agriculture may predispose farmers to different types of cancers.<sup>23-25</sup>

#### Past Medical and Social History

In the present study, only 6.5% of the patients had phimosis, contrary to higher frequencies between 25%-60% reported previously in patients with penile cancer.<sup>5,9</sup> In a study by Madsen et al., phimosis was significantly associated with the risk of penile squamous cell carcinoma (odds ratio [OR] = 3.39).<sup>26</sup> In fact, circumcision, which eliminates the risk of phimosis, has been found to be a protective factor in the development of invasive penile cancer.<sup>12,16</sup> In this study, there was possibly an underreporting of patients with phimosis due to incomplete data input of the physical examination findings in the patient records, similar to what occurred with schooling and other variables, so awareness in research for health personnel including medical students is required.

Most patients (90.9%) had never undergone circumcision at diagnosis, which supports the previously reported strong association between undergoing circumcision at birth or during childhood and the lower risk of penile cancer (OR = 0.41).<sup>10,16</sup> Nevertheless, circumcision does not act as a protective factor in all cases, since it reduces the risk of cancer mainly in patients

who have a preexisting condition of phimosis.<sup>12</sup> It is proposed that phimosis triggers inflammatory processes and the development of chronic injuries by facilitating the chronic irritation of penis mucosa by the smegma components.<sup>12,13</sup>

The present research found that the two patients with history of circumcision had a higher rate of recurrence ( $p=0.015$ ). This could probably be explained by the fact that in our environment circumcision is usually performed under certain medical conditions (cancer precursor lesions, foreskin tightness, phimosis, or inflammation of the foreskin), which represent all important factors not only for the development but also for the severity of penile cancer.<sup>12,13,16</sup>

History of STDs was reported by 13.3% of the studied patients, in contrast to previous findings where up to 76% of patients with penile cancer had a STD history.<sup>19</sup> The prevalence of HPV infection in patients with penile cancer has been found to be between 15% and 71%, with most of them having the basaloid or warty specific histological subtypes and the HPV16 and HPV18 serotypes.<sup>12,28,29</sup> However, in this study, no HPV infections were found, probably due to the lack of microbiological studies for HPV in the institution where the study was carried out. With regard to the finding of more frequent history of STDs in younger men, several factors may be involved, including a recall bias in older people and the absence of a clear diagnosis or empirical treatment of possible STDs in older patients.

This research showed that most patients with penile cancer (90.9%) have a smoking history. The use of tobacco in any form as a risk factor for penile carcinoma has been described in several studies.<sup>5,12,15,19</sup> Chaux et al., found that 76% of patients with penile cancer in Paraguay reported past or present consumption of tobacco, mainly in the form of cigarettes, and 55% of them still held the habit during the time of the study.<sup>19</sup> Smoking seems to have an important role in cases where cigarette smokers have been diagnosed with penile carcinoma, although it may be more important in the advanced stages of progression.<sup>12</sup>

Most patients (78.6%) reported an evolution time around 2 and 24 months, which is akin with previous reports that identified the delay in care as a very common feature in these patients, where between 25%-50% live with the injury for more than a year before being diagnosed.<sup>27</sup>

### **Clinical Characteristics of Penile Cancer**

It was found that 41.3% of patients had the penile shaft involved, differing with most of the scientific reports that identified the body of the penis as the least common site of cancer, accounting for less than 5% of the cases.<sup>8,26</sup> This could be explained by the level of complexity of the study center and the low social and economic resources of the population, which may cause the patients to carry the disease to more advanced stages. In our study, 27.5% of patients presented with involvement of more than one region of the penis, similar to a previous study which reported that up to 50% of the cases affected more than one penile structure.<sup>19</sup>

The study conducted in the same institution as the present study in the previous decade (1990-2000) reported a frequency of 71.3% for stage T2 diagnosis.<sup>17</sup> In the present research, 50% of the cases had a T2 or T3 stage diagnosis. Although this indicates that the majority of patients still present to physicians at an advanced clinical stage, it also shows a decrease of diagnoses at these stages and, possibly, a better care and disease management in the present time. Therefore, follow-up studies that analyze the incidence and presentation of penile cancer in the city are required to evaluate the disease progression and management of patients over the course of the disease.

A higher frequency of metastasis in patients with nodal involvement can be associated with the fact that penile cancer is a malignancy that progresses in a local-regional fashion, involving inguinal and pelvic lymph nodes before developing distant metastases.<sup>8,14</sup>

In our study, patients with a history of STD presented with an ulcerative lesion more frequently than patients with no history of STD, and the association was statistically significant. However, an association between history of STDs and the type of penile cancer lesion has not been previously reported.

### **Treatment**

The pharmacological management given in higher proportion to patients with metastases (28.6%) is consistent with previous reports that showed an increased survival rate in patients with advanced stages that receive chemotherapy.<sup>30,31</sup> Of those patients who underwent radical amputation (20%) in our study, 55% also had lymph node dissection and 77% had an ulcerative type of cancer presentation. This can be correlated with the facts that more advanced stages of the disease present with a greater involvement of lymph nodes and that ulcerative lesions are usually more infiltrative and therefore require a more radical treatment.<sup>8,31</sup>

Many of the results in this study are consistent with those described in the work of Ramirez et al., which was performed in the period 1990-2000 at the Hospital Universitario del Valle.<sup>17</sup> Although the number of cases identified over the same study period (10 years) was lower in our study (46 vs. 59), in both studies the predominant histologic type was squamous cell type carcinoma (95.7% and 100%), history of smoking was found in most of the patients (65.5% and 87%) and lack of circumcision was associated with the development of penile carcinoma (90.9% and 80%).

One of the limitations of this study is that the study was conducted at a tertiary-level referral institution, which traditionally serves low-income population, so the results cannot be extrapolated to the rest of the Colombian population. However, the results reveal the most important features of these patients, which may facilitate their identification and subsequent management. In this sense, this study presents a description of the cases evaluated without giving the occurrence or incidence of the event in the city of Cali.

Additionally, the nature of the study and the limitations of a retrospective study based on medical records review have to be taken into account. These limitations are mainly due to the loss of data, lack of information on medical records and failure to investigate risk factors and variables of interest. Certain variables that could have increased the significance of the association hypothesis were not included. In the case of smoking, the starting age or the Index of Packs per Year (IPA) was not taken into account. Regarding the sociodemographic variables, addressing the patient's salary or socioeconomic status would be useful to establish a stronger association between poverty and penile cancer. Knowing the total number of sexual partners or the age of the first intercourse would provide information on further exposure to behaviors that increase the risk of STDs and therefore penile cancer. There was no information regarding the hygiene habits of the patient, which has been widely associated with the development of penile cancer.<sup>19</sup>

Most of the results found in this study agree with those previously reported in the scientific literature; however, many of the limitations encountered during this project were related to the poor handling of the medical records and with it the great amount of valuable data lost. Therefore, it is necessary to remind the medical staff responsible for filling out the medical records about the importance of recoding minimally necessary data, including sociodemographic characteristics. In this way, more robust studies and the establishment of significant risk factors can be made.

As a conclusion, most of the patients with penile cancer found at this referral center had old age, history of tobacco use and lack of circumcision. The patients who presented in more advanced stages of the disease with lymph node metastasis had to undergo more radical procedures and presented a greater rate of recurrence compared with those with no lymph node involvement. Further research to establish associated factors and test the proposed hypothesis resulted from this study are needed to enable a better understanding of penile cancer.

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## Acknowledgments

To Ivan Escobar for his critical revision to the manuscript.

## Conflict of Interest Statement & Funding

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

## Author Contributions

Conception and design the work/idea: LMR, MMH, ALRJ, AJBP, FJBE. Collect data/obtaining results: LMR, MMH, ALRJ. Analysis and interpretation of data: LMR, MMH, ALRJ, FJBE. Write the manuscript: LMR, MMH, ALRJ, FJBE. Critical revision of the manuscript: LMR, MMH, ALRJ, AJBP, FJBE. Approval of the final version: LMR, MMH, ALRJ, AJBP, FJBE. Contribution of patients or study material: AJBP. Statistical advice: FJBE. Administrative or technical advice: AJBP, FJBE.

## Cite as:

Rengifo LM, Herrera M del M, Rincon-Jimenez AL, Bermudez-Pupo AJ, Bonilla-Escobar FJ. Penile Cancer in Cali, Colombia: 10 Years of Casuistry in a Tertiary Referral Center of a Middle-Income Country. *Int J Med Students*. 2014 Jul-Oct;2(3):109-14.



# Feeding Practices among Infants in a Rural Community in Bangladesh: A Cross-Sectional Study

Rajat Das Gupta.<sup>1</sup>

## Abstract

**Background:** Proper feeding practices during infancy are necessary for the growth and development of infants and to prevent malnutrition. This study was conducted to describe the feeding practice among infants in a rural area in Bangladesh. **Methods:** A cross-sectional study was conducted between February and June 2013. Data was collected through face-to-face interviews of 212 mothers using a pretested questionnaire. **Results:** Exclusive breast feeding and complementary feeding rates were 40.6% and 97.3%, respectively. One third of the mothers practiced prelacteal feeding, and honey was the most common item. Maternal illness (72.7%) was the most common reason for not giving breast milk. Infant formula was used as an alternative food in majority of the cases (72.7%). **Conclusion:** Percentage of exclusive breast feeding was not satisfactory. Encouragement of female education is recommended to improve feeding practices and infant care.

**Keywords:** Breast Feeding, Infant, Feeding Behaviour, Bangladesh, Hand Disinfection (Source: MeSH-NLM).

## Introduction

Infancy is defined by pediatricians as the time from birth until one year of age. The word itself is of Latin origin and means “unable to speak”. This period is very critical, as it represents the earliest stage of rapid physical growth and acquisition of gross and fine motor skills (including sitting without assistance, walking while holding on to furniture and using pincer grasp) and cognitive functions (including imitating gestures and using familiar objects properly).<sup>1,2</sup>

Proper feeding practices during infancy are essential for initiating and maintaining good health, nutrition and development of infants.<sup>3</sup> According to the latest World Health Organization (WHO) statistics, 45% of deaths during infancy are due to under-nutrition (Available from: <http://www.who.int/mediacentre/factsheets/fs342/en/>, updated 2014 Feb; cited 2014 Oct 10).

Morbidity and mortality secondary to poor nutrition can be prevented through good feeding practices during the first two years of human's life.<sup>4</sup> Breast feeding provides infants with ideal nourishment, stimulates their immune system and protects them from various infections and diseases. Breast feeding also improves response to vaccinations and provides many health-enhancing molecules, enzymes, proteins, and hormones, which are present in both the colostrum and breast milk.<sup>5</sup> Colostrum is the milk produced in late pregnancy and the first 2-3 days postpartum.

Unfortunately, in the majority of cases, exclusive breast feeding is not practiced in Bangladesh. Most of the neonates in Bangladesh receive prelacteal feeding, which is food given to neonates before the initiation of lactation. Prelacteal feeding includes sugar water, honey, or milk other than breast milk.<sup>3</sup>

Many studies have been conducted to evaluate the feeding practices among infants in Bangladesh. However, there have been no studies conducted that show feeding practice patterns. This study was conducted to describe the feeding practices among infants in a rural community of Bangladesh. The results may be used to recommend the necessary steps to be taken by the authorities to improve early nutrition in infants.

## Methods

A cross-sectional study was conducted between February 2013 and June 2013 in Gopalpur union under Begumganj Upazila (sub district) of Noakhali district in Bangladesh. The initial population included any mothers with infants. Mothers willing to take part in the study were included after giving informed consent. Mothers who were not willing to take part in the study were excluded. Given that the national rate of exclusive breast feeding in Bangladesh is quoted at 25% and considering a confidence interval of 95%, the sample size should be 288.<sup>6</sup> Of the 710 households in the Gopalpur Village, 300 households were sampled using systematic random sampling. Only 212 mothers were willing to take part in the study and that was the final sample size.

Data were collected through face-to-face interviews of the respondents with the help of a pretested semi-structured interview schedule. There were two parts: questions relating to socio-demographic characteristics and questions related to feeding practices. The questionnaire was validated (unpublished data) and a biostatistician was consulted. Written informed consent was taken from the respondents. Data was entered into Microsoft Office Excel® software in codes and analysis was done by SPSS software version 14.0®. Descriptive statistical analysis, which included frequency, mean and percentages, was used to characterize the data.

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Submission: May 5, 2014  
Acceptance: Sep 15, 2014  
Process: Peer-reviewed

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Approval for this study was obtained from Dhaka Medical College Ethics Committee. The author followed the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement in writing this article.<sup>7</sup>

## Results

The majority of the infants were between nine months to one year of age. The majority of the mothers (91 mothers, 42.9%) were educated up to the secondary level and 53 mothers (25.0%) were educated up to the primary level. The majority of the fathers (30.7%) received education up to the secondary level, and 46 fathers (21.7%) received primary education. The numbers of illiterate fathers and mothers were 17 (8.0%) and 13 (6.1%), respectively. The study revealed that 13.7% of fathers and 13.2% of mothers could only sign their names.

The majority (94.8%) of the 212 mothers surveyed breastfed their infant (**Table 1**). The percentage of prelacteal feeding was 33.0%. The majority of the mothers who gave prelacteal feeding used honey (38.6%) and sugar water (30.0%). The rate of colostrum feeding to infants was 88.7%. The reason for not giving colostrum was mostly due to maternal illness (79.2%). The rate of exclusive breast feeding was 40.6%, with 97.3% of mothers starting complementary feeding when their infant reached six months of age. The most common reason for not giving breast milk was maternal illness (72.7%). Among the 11 mothers who did not breast-feed their infants, 72.7% gave infant formula and 27.3% gave cow's milk. For giving alternate food, 45.5% mothers bottle-fed their infants, while the rest used a bowl and a spoon. In regard to the method of cleaning feeding utensils, 27.3% mothers used only water and 72.7% mother used soap and water. Before feeding the infants, 96.2% of mothers washed their hands. For those who washed their hands, 34.3% used only water, while the rest used soap water.

## Discussion

Proper feeding practices during infancy are essential, and the maintenance of these practices is encouraged worldwide due to its positive impact on child health.<sup>3</sup> This study reveals that among the type of pre-lacteal feeding, honey (38.6%) and sugar water (30.0%) were the most common. A study conducted in Thailand showed that mustard oil was the most common type of prelacteal feeding (42.9%), with honey (23.6%), sugar water (3.2%) and other types of food (26.7%) being used as well.<sup>8</sup>

The percentage of mothers who gave colostrum to their infant was 88.7% in this study. This finding differs from a study conducted in the outpatients department at a tertiary hospital in Bangladesh in 2009, which showed that 79.2% of mothers gave colostrums to their infants.<sup>9</sup> This is an encouraging result and suggests that the awareness among the mothers regarding providing colostrum to infants is increasing. However, this difference may also be due to place and time discrepancy.

Among all infants, 94.8% were breastfed. This finding is consistent with another study conducted in rural Bangladesh, where 99.4% of the mothers breastfed their infants.<sup>10</sup>

The study reveals that 70.8% infants were breast-fed within one hour of birth. In a study published in 1996, only 9% of mothers had initiated breast feeding immediately after birth.<sup>10</sup> Another

**Table 1.** Feeding practices among infants.

Categories	Freq.	%
Pre-lacteal feeding practices (n=212)	70	33.0
Type of pre-lacteal food (n=70)		
Honey	27	38.6
Sugar water	21	30.0
Water	4	5.7
Others	18	25.7
History of giving colostrum (n=212)	188	88.7
Causes of not giving colostrum (n=24)		
Mother's illness	19	79.2
Ignorance	05	20.8
History of Breast Feeding (n=212)	201	94.8
Causes of not giving breast milk (n=11)		
Mother's illness	8	72.7
Lack of breast milk	3	27.3
Type of food alternate to breast milk (n=11)		
Infant Formula	8	72.7
Cow's Milk	3	27.3
Type of utensil used for giving food alternate to breast milk (n=11)		
Bowl & spoon	6	54.5
Bottle	5	45.5
Method of cleaning the utensil (n=11)		
Soap and water	8	72.7
Only water	3	27.3
Time of starting breast-feeding (n=201)		
Within 1 hour	150	74.6
Within 24 hours	36	17.9
After 24 hours	15	7.5
Feeding practices of mother for their infants up to 6 months (n=212)		
Breast milk & supplementary food	115	54.3
Only breast milk (exclusively breast feeding)	86	40.6
Only supplementary food	11	5.2
History of starting complementary feeding after 6 months (n=86)	84	97.3
Hand washing practice before feeding the infant (n=212)	204	96.2
Hand washing technique (n=204)		
Water and soap	134	65.7
Only with water	70	34.3
Washing of utensil before infant feeding (n=206)	202	98

study conducted in a rural area of Bangladesh in 1996 showed that 73% of mothers initiated breast feeding within the first two days.<sup>11</sup> But national findings in Bangladesh showed that only 43.0% newborns are put to breast right after birth.<sup>4</sup> These encouraging results suggest that the awareness of the benefits of breast feeding among mothers has increased.

Regarding feeding practices, the majority (54.3%) of mothers fed their infants breast milk along with supplementary food. Bengal national figures shows that only 25.0% mother exclusively breast-fed their infant by the fourth month of their li-

ves, compared to 40.6% of mothers in the current study. Other studies reported that approximately one third of mothers exclusively breastfed their infants until two to three months of life.<sup>3,5,12</sup> These results show that the prevalence of exclusive breast feeding has improved.

Furthermore, 97.3% mother started complimentary feeding after six months. However, this finding is inconsistent with another study which was conducted between 2001-2003, where 66.7% of infants were fed with complimentary food. This discrepancy may be due to time factor between the two studies. Mothers may now be more aware of the need to provide complementary food.<sup>3</sup>

For giving alternate food, 45.5% of mothers used bottle and the rest used a bowl and a spoon. In regard to the method of cleaning feeding utensils, 27.3% of the mothers used only water and 72.7% used soap and water. This finding reflects their knowledge on the importance of cleanliness in preventing diseases. It may also be due to their access to cleaning supplies.

The study findings showed that before feeding the infants, 96.2% of mothers washed their hands. For those who washed their hands, 34.3% used only water, while the other 65.7% used soap water. Used utensils were washed before feeding by 98% of mothers. A study published in 2008 showed that fewer than

5% of caregivers wash their hands with soap before feeding babies.<sup>13</sup> This also reflects their knowledge on the importance of hand washing. This is probably due to effective communication messages and easy availability of water and soap as showed in a study performed in Bangladesh in 2011.<sup>14</sup>

The study has several limitations. First of all recall bias may exist. Data were collected from a part of selected rural community and may not reflect the whole scenario of feeding practices in rural communities of Bangladesh, limiting the generalizability of the results. The target sample size could not be reached, and this represents another limitation. Nevertheless, this study is the first study on infant feeding practices conducted in the study area. Larger studies should be carried out to reveal the whole scenario of feeding practice in rural communities in Bangladesh and other developing countries to improve the healthcare of children.

The study demonstrates that most mothers breastfeed their infants. The percentage of giving colostrum to the infants was satisfactory. The percentages of hand washing and cleaning of utensils were also satisfactory. As the rate of exclusive breast feeding was not satisfactory, measures should be taken to promote female education and to raise awareness among the population about the importance of exclusive breast feeding during the first six months of life.



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## Acknowledgments

I am grateful to Dr. Nirmin Rifat Khan, Associate Professor, Community Medicine, Dhaka Medical College, Dhaka University, Bangladesh; Dr. M Tasdik Hasan Dip, Research Fellow, The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) and Dr. Gourab Adhikary, Research Fellow, The International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) for their guidance and support.

## Conflict of Interest Statement & Funding

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

## Author Contributions

Conception and design the work/idea, Collect data/obtaining results, Analysis and interpretation of data, Write the manuscript, Critical revision of the manuscript, Approval of the final version, Contribution of patients or study material, Obtaining financing, Statistical advice, Administrative or technical advice: RDG

## Cite as:

Gupta RD. Feeding Practices among Infants in a Rural Community in Bangladesh: A Cross-Sectional Study. *Int J Med Students*. 2014 Jul-Oct;2(3):115-8.

# The Atopic March. A Literature Review

Juan F. Salazar-Espinosa.<sup>1</sup>

## Abstract

The atopic march is defined as the progression of atopic diseases, generally during childhood, such as atopic dermatitis, asthma, allergic rhinitis and food allergies. The main risk factors for developing these atopic diseases include genetics, aeroallergens, food allergens, late food introduction to the infant, and living in developing countries. The immunologic contributors to this problem include the Th2 response, epigenetics, and lack of certain factors like thymic stromal lymphopoietin (TSLP) and filaggrin. As a whole, the therapeutic approach has been changing during recent years because of the discovery of new factors involved in this problem. This article explains the definition of atopic march, the immunological pathway, clinical features, epidemiology and therapeutic approaches to create a context for the broader understanding of this important condition.

**Keywords:** Atopic dermatitis; asthma; allergy; atopy; Th2 response; atopic march (Source: MeSH, NLM)

## Introduction

Atopic march is an epidemiological phenomenon involving atopic diseases and describes the process by which some atopic diseases interrelate through a patient's life. These atopic diseases include asthma, atopic dermatitis (AD), allergic rhinitis, and food allergies. The common progression of these diseases is from atopic dermatitis to asthma and then allergic rhinitis; this is not, however, the only way that this condition progresses. The atopic march has some associated risk factors that have been described in epidemiological studies from different countries. There exist, however, some differences in the disease epidemiology depending on the socioeconomic status of the country studied.<sup>1</sup>

The pathogenesis of the atopic processes share a common systemic Th2 response and epigenetic factors. Related to Th2 response are other immunological factors like filaggrin deficiency and thymic stromal lymphopoietin (TSLP) overexpression which have been demonstrated in mouse models and serve as therapeutic targets.<sup>2</sup> These exist in addition to the ratio between histone acetyl transferase (HAT) and histone deacetylase (HDAC) as the most important epigenetic factors involved in allergies.<sup>3</sup> The therapeutic approach has multiple pharmacological options, including subcutaneous and sublingual immunotherapy, prebiotics, probiotics and, most recently, anti-IgE monoclonal antibodies. The multitude of therapeutic approaches seen in atopic march may be explained by the observation that there are different preferences for various treatments among different medical specialties.<sup>4</sup>

## Search Strategy and Selection Criteria

A literature search was performed using MEDLINE MeSH ter-

ms "eczema", "asthma", "food allergy" and "allergic rhinitis" where each term was combined with "atopic march" using the PubMed search builder. A total of 177 articles were found. Following filtering by author criteria (publication within last 20 years, English language, and the existence of a relation between at least two atopic diseases), 32 articles remained and an additional 22 articles were retrieved from references. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.<sup>5</sup>

## Immunological Pathway

The first step in atopic march pathogenesis is allergen exposure or the first sensitization episode in a patient's life, leading to the activation of the epithelial cell triggers and the release of TSLP and tumor necrosis factor alpha (TNF- $\alpha$ ). These are chemotactic factors for dendritic cells, which induce the expression of adhesion molecules at the endothelium.<sup>6</sup> Dendritic cells internalize the allergen through their high affinity IgE receptors (Fc $\epsilon$ RI) and migrate and mediate the naïve T cell activation in Th1 cells, which releases interleukin-2 (IL-2) and interferon-gamma (IFN- $\gamma$ ), and Th2 cells, which releases IL-4, in the lymph nodes. Following this is a process called scratch-rubbing cycle where a skin barrier dysfunction (filaggrin mutations) leads to a decrease in Th1 response and an increase in Th2 response with the release of IL-5 and IL-13. This triggers the increase in eosinophilic infiltration with an immunoglobulin E (IgE) hyperproduction. The Th2 response enhances the allergen response in the nasal and bronchial mucosa, leading to eosinophil infiltration and IgE hypersecretion in addition to the mast cell proliferation, epithelial cell activation, mucus hypersecretion, and smooth muscle proliferation observed in asthma.<sup>7,8</sup>

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Submission: Mar 18, 2014  
Acceptance: Aug 22, 2014  
Process: peer-reviewed

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Filaggrin is a protein produced in the stratum corneum of the epidermis that plays an essential role in the formation of the protective skin barrier by the prevention of water loss and entry of microbes into the inner layers of the skin. The main mechanism that involves filaggrin in the allergic disease pathogenesis is the enhancement of the Th2 systemic response, which leads to the susceptibility of skin, bronchial, nasal, and gastrointestinal epithelia to the development of atopic diseases, especially atopic dermatitis and asthma.<sup>9</sup> Importantly, it has been discovered that the maintenance and repair of the epidermal barrier in infants with AD may prevent the subsequent development of asthma.<sup>10</sup>

The TSLP is an IL-7-like interleukin which is produced in the skin, gut, lungs and thymus and contributes to the activation of dendritic cells without the allergen molecule, the predominance of Th2 differentiation, and the upregulation of this response by the mast cells in the nasal epithelium, leading to the development of allergic rhinitis.<sup>11</sup> **Figure 1** shows the process involved in the generation of atopic march and some of the factors that may contribute to the development of atopic diseases.

Takai et al., suggested that environment, infection, and/or self-derived toll-like receptor ligands contribute to the initiation and/or amplification of Th2-type skin inflammation, including atopic dermatitis, through the induction of TSLP expression in keratinocytes. This finding is helpful for understanding the role of the gene-environment interaction relevant to allergic diseases.<sup>12</sup>

One of the main factors in the epigenetics of the atopic march is GATA-3, which is activated by T-cell receptor (TCR) and IL-4 receptor activation and maintains its own expression through positive feedback. GATA-3 induces permissive histone and chromatin changes at the Th2 Locus Control Region (LCR) which enhances the Th2 response and suppresses the Th1 response against the allergens. Another important factor is FFOX3, which regulates the T regulator cell action by promoting the binding of demethylation factors and the consequent lack of tolerance to self and exogenous antigens.<sup>3</sup>

## Mouse Models in Atopic March

Zhang et al., carried out investigations in which they injected

mice with intra-peritoneal ovalbumin and measured the TSLP produced by keratinocytes. TSLP is the mediator of the skin inflammation triggered by an allergen and consequent sensitization. Additionally, another mouse model demonstrates a relation between high skin keratinocyte-derived TSLP, high TSLP serum levels and the upregulated epicutaneous sensitization, and aggravated allergic asthma generated upon allergen challenge in airways.<sup>13,14</sup> However, Demrhi et al., demonstrated that during the first 3 years of life, the plasma circulating TSLP of children with eczema, allergen sensitization, or wheezing was not statistically associated with the manifestation of these symptoms.<sup>2</sup> The TSLP is implicated in mouse models for the development of atopic diseases. This supports the utilization of TSLP inhibition as a proposed therapeutic option to prevent or limit allergen sensitization and thus halt the progress of the atopic march.<sup>15</sup>

## Clinical Features

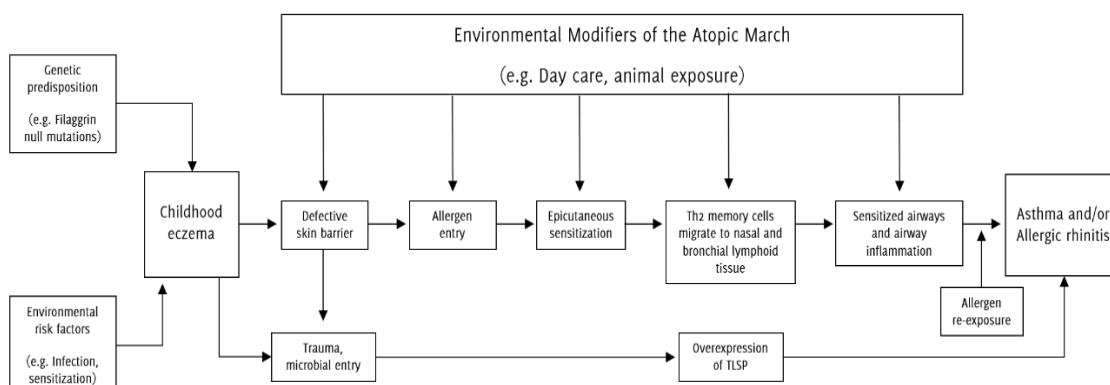
### Atopic Dermatitis

There are three established phases in the progression of AD: an infantile phase (from birth to 2 years of age), a childhood phase (2 years to puberty) and the adult phase (from puberty to the adulthood). The first manifestations correspond to erythematous papules and vesicles that typically begin on the face and are intensely pruritic. There is also edema of affected areas, leading to oozing and crusting. The childhood phase of AD additionally presents with lichenified papules and plaques, representing a more chronic disease. Lymphadenopathy might be a prominent feature in affected children. Although the disease sometimes tends to self-resolve, there is an adult phase of AD which predominantly involves the flexural folds, the face and neck, the upper arms and back, and the dorsa of the hands, feet, fingers, and toes. Weeping, crusting, and exudation might occur, usually as a result of superimposed Staphylococcal infection.<sup>10</sup>

### Asthma, Allergic Rhinitis and Food Allergy

A wide array of risk and protective factors including hygiene, infections, outdoor and indoor air pollution, allergen exposure, breast-feeding practices, genetic factors, nutrition, and obesity play a multifaceted role in shaping the observed worldwide trends of respiratory allergies.<sup>16</sup> Some of these patients never present with any clinical symptoms throughout their lives, although airway hyperresponsiveness, shortness of

**Figure 1.** A proposed pathway to explain the atopic march from childhood eczema to the development of asthma and allergic rhinitis.<sup>4</sup>



Source: Dharmage SC, Lowe AJ, Matheson MC, Burgess JA, Allen KJ, Abramson MJ. Atopic dermatitis and the atopic march revisited. *Allergy*. 2014 Jan;69(1):17-27. Reprinted with permission from John Wiley and Sons.



breath, wheezing which causes chronic airflow limitation, and decreased lung function are common. Examinations of these patients reveal low forced expiratory volume in 1 second (FEV<sub>1</sub>) together with an increased eosinophil and Th2 infiltration in bronchial tissue. An Indian study shows that fractional exhaled nitric oxide (FeNO) is a marker of lower airway inflammation; therefore, significantly higher FeNO levels in atopic allergic rhinitis patients may predict the onset of asthma.<sup>17</sup> For allergic rhinitis, there are four main symptoms: watery rhinorrhea, nasal obstruction, nasal itching, and sneezing.<sup>18</sup> Like asthma, allergic rhinitis could be classified as mild or moderate-severe based on severity.<sup>19-21</sup>

Food allergy is known to be one part of this atopic process and its incidence tends to be higher at 2 years of life.<sup>22</sup> A clinically relevant event is cow milk allergy, which is proposed as a risk factor for the development of asthma, rhinoconjunctivitis and eczema.<sup>23</sup> Food allergy is clinically well characterized by urticaria, angioedema, vomiting or anaphylaxis. These clinical manifestations are present within two hours following the food ingestion. There are some foods that mediate this disease like peanuts, cow milk, and eggs. Besides these symptoms other clinical manifestations include a scratchy throat, hives anywhere on the body, swelling of the eyelids, face, or tongue, nausea, cramps, vomiting, diarrhea, nasal congestion, and shortness of breath or wheezing due to the exposure to a hapten of the food.<sup>24</sup> A controversial dilemma, which began in the 1970s and remains unresolved, includes whether the introduction of food antigens into the diet either early or later in life has any effect on the development of food allergy, atopy or allergic asthma. This is explained by the antigens present in the food (cow milk) which are captured by the Peyer patches and generate a Th1 response in healthy children.<sup>25,26</sup> Some studies concluded that the early food introduction and six months breastfeeding after birth are poor prognostic factors and predispose the infants to the development of food allergy.<sup>27</sup> However, a population-based prospective cohort study using 3781 children performed in 2013 established that long term breastfeeding and the early introduction (with specific timing) of wheat, rye, oats, barley cereals, fish, and eggs is preferred in that it protects against the development of asthma and allergic rhinitis from a few months following birth to the age of five. This finding suggests a potential conflicting effect of breastfeeding on different asthma phenotypes.<sup>28</sup>

### Epidemiology

There are three established progressive pathways in this process: (1) atopic dermatitis to asthma and allergic rhinitis, (2) asthma to atopic dermatitis, and (3) asthma to rhinitis without the presence of atopic dermatitis. Food allergy is an associated risk factor in the development of these three conditions, and for this reason it can be found in any phase of the atopic march. However, a reverse atopic march has been proposed, with patients developing asthma first with the later appearance of atopic dermatitis. This is demonstrated in a prospective study that followed nearly 700 children aged six to nine years with asthma alone for nine years. Twenty percent of the children developed atopic dermatitis at the end of nine years.<sup>29</sup>

Atopic dermatitis has a prevalence that ranges from 7% to 30% in children and from 2% to 10% in adults.<sup>30</sup> AD and food aller-

gies have the highest incidence in the first two years of life. Sensitization to inhalant allergens is rare at that time of life. In later childhood, the prevalence of AD and food allergies decreases while the prevalence of asthma, allergic rhinitis, and sensitization to inhalant allergens rises.<sup>31</sup> Shen et al., followed a birth cohort for seven years and classified the eczema into preschool and late-onset and examined the correlation between the development of asthma and allergic rhinitis. Results showed that the 36 month old group (late-onset group) had the highest risk for developing asthma or allergic rhinitis five years later. This indicates that it is necessary to evaluate the associated risk factors at the first presentation of atopic disease in order to predict its progression in subsequent years.<sup>32</sup>

A longitudinal study of a prospective birth cohort of 620 children described a higher prevalence of atopic march in boys than girls by a mechanism that remains unknown.<sup>33</sup> Higher body mass index (BMI) is a risk factor for atopy, wheezing, and cough in girls only.<sup>34</sup> However, higher BMI is not a risk factor for asthma or airway hyperresponsiveness in either boys or girls. As the atopic march is a disease of interrelation, the etiology is not the same for all components. In fact, it is described that parents with asthma give birth to children with four times the odds of developing food allergy.<sup>35</sup> The food allergy is associated with six times the odds of developing asthma compared to patients without any food allergy.<sup>36,37</sup>

It is believed that developed countries have reached a plateau in the incidence of asthma while in developing countries the incidence of these diseases is still increasing.<sup>16</sup> Van der Hulst et al., conducted a systematic review which assessed the risk of developing asthma in children with atopic eczema during the first four years of life and found that the prevalence of asthma at the age of six years in eczema cohort studies was 35.8% for inpatients and 29.5% for a combined group of inpatients and outpatients.<sup>38</sup> A Norway study, with 4780 children divided into two groups depending on whether they were followed from two years old to six years old (n=2192) or not followed (n=2588). Among children with follow-up data at six years, the prevalence of eczema, asthma, and wheezing at two years was 17.8%, 6.5% and 25.3%, respectively. Among children with follow-up data at six years, the odds ratio between eczema at two years and current asthma at six years was 1.95. When the age of onset for eczema was included in the model, an onset before four months of age was significantly associated with asthma at six years (OR= 4.51).<sup>39</sup>

Meanwhile, in middle-income countries, a study conducted during the 2009-2010 period in Colombia collected information from 5,978 patients and analyzed three principal atopic diseases: allergic rhinitis, atopic eczema and asthma. It was discovered that 12% of the patients had asthma, 32% had allergic rhinitis and 14% had atopic eczema and demonstrated an increased presentation of symptoms characteristic of these conditions.<sup>40</sup> In Taiwan, Hwang CY et al., collected longitudinal cohort information through the medical institution databases that followed patients for eight years. Overall, 66,446 patients were diagnosed with atopic dermatitis and 49.8% of them had concomitant allergic rhinitis and/or asthma. The overall 8-year prevalence of atopic dermatitis, allergic rhinitis, and asthma was 6.7%, 26.3% and 11.9%, respectively.<sup>41</sup> In addition, Waked

et al., administered standardized written questionnaires to 5- to 12-year-old students at 22 schools. In total, 3,909 individuals were analyzed. The prevalence of diagnosed asthma (4.8%) was low, while the prevalence of allergic rhinitis was 21.2% and that of eczema was 11.8%. Marked variations and differences were found across the governorates in Lebanon, with the lowest prevalence of diagnosed asthma found in Bekaa (1.8%) and the highest prevalence in Beirut (11.6%).<sup>42</sup> The differences in the prevalence of atopic diseases between developing and developed countries likely reflect the differences in the extent of urbanization, industrialization, life style, latitude, and disease severity. Other possible factors, such as socioeconomic status or ethnic group, may also contribute to this variation.

### Therapeutic Approaches

Gordon BR et al., suggested that it is possible to interrupt the atopic march to prevent allergy, especially asthma, with three possible interventions: (1) supplements of dietary probiotics, (2) exclusive breast feeding during the first few months of life, which provides protection from the development of allergies through the high transforming growth factor beta (TGF- $\beta$ ) levels in breast milk, and (3) treatment with inhalant allergen immunotherapy by either subcutaneous or sublingual immunotherapy, both of which decrease the risk of progression to asthma and allergic rhinitis. From current data, if these strategies were widely employed, there would likely be a substantial reduction in future asthma cases.<sup>43</sup> This is supported by the 2013 PRACTALL trial, which has established a subcutaneous immunotherapy and a sublingual immunotherapy for allergic asthma and rhinitis based on scores given for symptom reduction, improvement in quality of life, and the induction of favorable changes in specific immunologic markers.<sup>44</sup> In a randomized controlled trial, Passalacqua et al., found immunotherapy for allergic rhinitis to be a preventive factor for asthma development due to the impairment of new sensitizations.<sup>21</sup>

Anti-IgE treatment with omalizumab is another therapeutic option used for rhinitis where its mechanism of action is by specifically binding to IgE with the consequent interruption in the allergic response. New information suggests that the combination of immunotherapy with omalizumab is a good strategy to treat allergic rhinitis.<sup>45</sup> However, when the monoclonal antibody XmAb7195, human leukocyte-engrafted mouse like omalizumab, was administered, it selectively reduced serum human IgE levels and was much more effective than omalizumab in suppressing IgE levels by dual pathways involving IgE neutralization and a CD32b-dependent inhibition of the formation of IgE-secreting plasma cells. This demonstrates new advances in therapeutic approaches by inhibiting one of the main factors in the development of atopic diseases (i.e. IgE).<sup>46</sup>

Prebiotics, probiotics and breast feeding balance the “Th2 bias”, thus improving intestinal processing of antigens ingested in the diet and reducing intestinal inflammation and IgE production by increasing the uptake of antigens by Peyer’s patches. This prevents the development of a Th2-exaggerated immune response which would lead to the systemic sensitization and major enhancement and distribution to tissues like bronchial tissue.<sup>47</sup> Breastfeeding is recommended to be complemented with probiotics because it increases the number of of immunoglobulin secretor cells, which is one of the main

factors involved in protection against atopic problems.<sup>48</sup> It is theorized that probiotics act at the Clostridium/Bifidobacterium ratio by increasing the Bifidobacterium populations.<sup>49</sup> Moreover, according to Vitaliti et al., the use of probiotics induces the enhancement of regulatory cell responses to produce more anti-inflammatory cytokines which may decrease the likelihood of the development of allergies.<sup>50</sup> In 62 mother-infant pairs, *Lactobacillus rhamnosus* GG administered during the four weeks before the infant’s birth and during breast feeding (first three months) increased the immuno-protective potential of breast milk, as assessed by the enhancement of anti-inflammatory TGF- $\beta$ 2 in the milk of the mothers receiving probiotics vs. placebo.<sup>51</sup> Furthermore, the probiotics are considered to be the main factors involved in the prevention of atopic march.<sup>52</sup> Prebiotics are nondigestible food products (most commonly oligosaccharides) that stimulate the growth or activity of Bifidobacteria and other “friendly” bacteria in the colon. However, further research is needed before routine use of prebiotics can be recommended for prevention of allergy in formula fed infants. It is unclear whether the use of prebiotic should be restricted to infants at high risk of allergy or whether they may have an effect in low risk populations or on other allergic diseases including asthma.<sup>53</sup>

### Conclusion

New information constantly expands our understanding of allergen-induced diseases; this information is reflected in epidemiological studies which demonstrate a non-linear development and relationship of the various components of the atopic march. The atopic march should be understood as an immunological imbalance in Th2 responses together with factors like the TSLP, lack of filaggrin, and epigenetics (FOXP3 and GATA-3). The epidemiologic data tends to be in accordance with data obtained using mouse models, which provide insights to the development of additional epidemiologic studies. In regard to the therapeutic approach, atopic march should always be understood as a multiple-disease problem and not simply as a single atopic disease. The monoclonal antibodies, sublingual therapy, immunotherapy, prebiotics and probiotics are proving to be promising therapies which need further investigation to demonstrate their action against the immunological factors involved in this disease.

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**Acknowledgments**

None.

**Conflict of Interest Statement & Funding**

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

**Author Contributions**

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

**Cite as:**

Salazar-Espinosa JF. The Atopic March. A Literature Review. *Int J Med Students*. 2014 Jul-Oct;2(3):119-24.

# The Role of Chemotherapy and Radiotherapy in the Surgical Management of Muscle Invasive Bladder Cancer

Joshua Luck.<sup>1</sup>

## Abstract

The management of muscle invasive bladder cancer represents an unresolved clinical challenge. Invasive urothelial carcinomas are associated with high mortality rates and early metastatic disease. Radical cystectomy is a recognized standard of care, although disease-free survival outcomes remain suboptimal. The limitations of pre-operative clinical staging, as well as the complex natural history of the disease, precludes the introduction of simple management protocols. To what degree chemotherapy and radiotherapy may be useful in the surgical management of invasive bladder cancer remains contentious. This literature review critically examines the benefits, risks and difficulties of each approach, with an emphasis on individually tailored therapy.

**Keywords:** Chemoradiotherapy, combined modality therapy, urinary bladder neoplasms, cystectomy (Source: MeSH, NLM).

## Introduction

Bladder cancer is the fourth most common malignancy in men and the ninth most common in women, with an estimated incidence of 32.5 per 100,000 in the West.<sup>1</sup> The overwhelming majority of bladder cancers in this population arise from urothelial epithelium; approximately 90% are transitional cell carcinomas (TCC). Rarely, squamous cell carcinoma or adenocarcinoma may be seen, in 7% and 2% of cases respectively (although their prevalence is subject to certain geographical parameters). The etiology of bladder cancer remains controversial and various risk factors have been identified, discussed elsewhere.<sup>2</sup> <sup>3</sup> Patients are typically elderly (>65 years) and male: few cases are seen below the age of 50 and men are four times more likely to develop the condition.<sup>4</sup>

The management of bladder cancer remains controversial. Indeed, falling bladder cancer incidence over the last two decades has not been associated with universal improvements in mortality.<sup>5</sup> This literature review will critically appraise the use of chemotherapy and radiotherapy in the surgical management of muscle invasive bladder cancer. Multimodal therapies for non-invasive and metastatic disease fall beyond the scope of this topic. Similarly, specific surgical approaches will only be discussed where appropriate.

## Search Strategy and Selection Criteria

A literature review was performed using PubMed, MEDLINE, Science Direct, Scopus and Embase databases using the search terms 'muscle invasive bladder cancer', 'radical cystectomy', 'bladder-sparing surgery' and 'chemotherapy/radiotherapy for bladder cancer'. Randomized studies, reviews and consensus guidelines were included. Additional relevant papers were retrieved from the references. All included articles were in the English language. This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.<sup>6</sup>

## Stage and Grade

The primary determinant of prognosis is the stage and grade of the lesion, with lesser concern given to size and multicentricity for muscle invasive disease.<sup>7</sup> Clinical staging is based upon a standard TNM classification system.<sup>8</sup> Most tumours (~70%) are non-muscle invasive and, of these, about 70% are confined to the bladder mucosa.

T2 lesions and above are described as 'invasive', having infiltrated the superficial muscle layer at least. Muscle invasion is related to significantly worse outcomes: the natural history (without treatment) in ~85% of cases is death within two years.<sup>9</sup> Additionally, the probability of nodal and metastatic disease is appreciably increased – around 5% of patients present with metastatic deposits. The TNM system for bladder cancer is outlined in *Table 1*.<sup>8</sup>

The accuracy of available methods for determining the degree of muscle invasion pre-operatively is relatively poor. In fact, the correlation between depth of invasion on cystoscopy and biopsy reports is only in the region of 70%.<sup>10</sup> The limitations of clinical staging are further illustrated in a study of 778 consecutive patients treated with radical cystectomy and pelvic lymphadenectomy: histological up-staging occurred in 42% of patients and down-staging in 22%.<sup>11</sup> However, tissue diagnoses themselves are not always reliable and there remains a significant risk of under-staging following initial resection. Indeed, some studies report that 4-25% of tumours originally classified as non-muscle invasive are actually muscle invasive.<sup>12,13</sup>

The detection of lymph node involvement using imaging techniques is similarly poor. About 20-30% of patients with node negative disease according to computerised tomography (CT) criteria will have pathologically positive specimens at lymphadenectomy.<sup>14</sup> Conversely, a proportion of cases with apparently node positive disease on CT or magnetic resonance imaging (MRI) will be downgraded at the time of surgery. An appreciation of these limitations may influence the relative authority given to surgery over chemotherapy or radiotherapy regimens.

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*Submission: Aug 1, 2014  
Acceptance: Oct 12, 2014  
Process: peer-reviewed*

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**Table 1.** TNM Stage & Grade Classification.<sup>9</sup>

Primary Tumour (T)	
TX	Primary tumour cannot be assessed
To	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumour"
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscularis propria
pT2a	Tumour invades superficial muscularis propria (inner half)
pT2b	Tumour invades deep muscularis propria (outer half)
T3	Tumour invades perivesical tissue:
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumour invades extravesical structures
T4a	Tumour invades prostatic stroma, uterus, vagina
T4b	Tumour invades pelvic wall, abdominal wall
Regional Lymph Nodes (N)	
NX	Lymph nodes cannot be assessed
No	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis
N2	Multiple regional lymph node metastases in the true pelvis
N3	Lymph node metastases to the common iliac lymph nodes
Distant Metastases (M)	
Mo	No distant metastasis
M1	Distant metastasis
Histological Grade (G)	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated

Source: Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media.

Both CT and MRI scans may be used to assess local invasion, although both techniques only reliably detect T3b (extra-vesical) disease or above.<sup>15</sup> Some debate has surrounded the relative authority given to MRI over CT; however, the greater soft tissue contrast afforded by the former now means it is the imaging modality of choice. For example, the accuracy of MRI in primary tumour staging is in the region of 85%, some 20% higher than CT.<sup>16</sup> There may also be a role for fast dynamic contrast-enhanced MRI, especially in differentiating tumour from post-biopsy reactive changes.<sup>17</sup> To avoid this, current consensus suggests that imaging be undertaken before resection in cases where muscle invasion is suspected.<sup>18</sup>

## Treatment Options for Muscle Invasive Bladder Cancer Surgery

Radical cystectomy with lymphadenectomy represents a recognized curative standard of care for muscle invasive disease, or high-risk superficial carcinoma unresponsive to conservative treatment. Bladder-preserving alternatives will not be discussed here, except to highlight that these conventionally employ a multimodal approach in which surgical resection is supported by post-operative chemoradiotherapy.<sup>19</sup>

Epidemiological studies repeatedly demonstrate that radical cystectomy produces the best outcomes, with recurrence free survival at

five years most marked in organ-confined invasive cancer.<sup>20,21</sup> Importantly, early cystectomy within a three-month window is associated with improved survival. In a subgroup analysis of patients with  $\geq T2$  carcinoma, one study showed significantly less progression to lymph node positive disease (12% vs. 26%;  $p < 0.013$ ) and enhanced five-year disease-specific survival (80% vs. 56%,  $p < 0.0006$ ) following prompt surgical treatment.<sup>20</sup> Within this 12-week timeframe, however, there appears to be no additional benefit of earlier local therapy.<sup>21</sup>

The factors influencing the type of urinary diversion offered are beyond the scope of this review; however, a recent Cochrane report suggests that no particular technique is convincingly superior.<sup>22</sup> Crucially, the type of reconstructive approach used has no significance with regards to whether chemotherapy or radiotherapy can be offered.<sup>3</sup>

The benefits of an initial surgical approach typically relate to tumour debulking and relief of local symptoms. Perhaps more importantly, surgical resection allows for definitive pathological staging. A larger, more recent trial to that discussed earlier demonstrated misleading clinical staging in 68% of the 3393 patients assessed.<sup>11,23</sup> Removed specimens may be used to establish chemosensitivity profiles, or to stratify the patient into specific risk groups (so as to better inform their decision as to whether to opt for additional therapies). For example, those with pT2 TCC can expect up to 80% recurrence free survival at five years without additional chemotherapy or radiotherapy.<sup>24</sup> Prompt tissue diagnosis is therefore beneficial in this regard.

## Chemotherapy: Neoadjuvant chemotherapy

Most bladder cancer patients usually succumb to distant disease. Long-term follow-up of radical cystectomy patients suggests that, despite adequate local control, overall survival for muscle invasive TCC is suboptimal. Only 52-77% of pT2, 40-64% of pT3 and 26-44% of pT4 individuals can expect to survive five years post-surgery.<sup>24</sup> Occult micrometastatic disease during definitive local therapy is thought to underlie these unsatisfactory outcomes; hence, a key benefit of pre-operative chemotherapy is that it may permit early treatment of outlying disease.

Neoadjuvant chemotherapy also allows for an in vivo assessment of tumour response (possibly leading to down-staging and reversion to bladder-sparing surgical options in a subset of patients). In one study of 111 patients with invasive TCC, 54% showed clear transurethral biopsies following MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) therapy.<sup>25</sup> These 60 patients were then allowed to choose between follow-up transurethral surveillance ( $n=28$ ), partial cystectomy ( $n=15$ ) or radical cystectomy ( $n=17$ ). Of the 43 who opted for bladder-sparing options, 74% were alive at ten years and 58% were fully continent. However, 56% developed recurrence and 13 cases required salvage cystectomy. These data demonstrate that the majority of locally advanced carcinomas responsive to chemotherapy are candidates for bladder-sparing intervention at a known risk of recurrence and, of these, most can be treated with salvage cystectomy.

Patient reported outcome measures suggest that conservative, bladder-sparing approaches are preferable to radical cystectomy. A questionnaire-based study of 59 patients demonstrated improved quality-of-life measures in all parameters assessed, the majority of these trends reaching statistical significance.<sup>26</sup> Thus, neoadjuvant treatment followed by bladder-preservation qualifies as a recognized standard of care for a subset of eligible patients. This may be offered to selected patients for their own consideration.



Even if bladder sparing does not become feasible, chemotherapy in the neoadjuvant setting appears to be largely beneficial. For example, the 1999 European Organization for Research and Treatment of Cancer (EORTC) Study suggests that pre-interventional chemotherapy is of value in both radical cystectomy and radical radiotherapy patients.<sup>27</sup> Median survival of patients randomised to the chemotherapy group increased from 37.5 months to 44 months following three cycles of CMV (cisplatin, methotrexate and vinblastine). Despite a higher incidence of pathological complete response in the treatment arm and this trend towards longevity, the failure to achieve a pre-defined 10% survival improvement criterion meant that these data were originally reported as unsuccessful. Importantly, however, seven-year delayed follow-up revealed a statistically significant hazard ratio (HR) of 0.85 in favour of chemotherapy. The later US Intergroup Trial (SWOG 8710) showed similar improvements in life expectancy: on intention-to-treat analysis of the 317 patients enrolled and randomised, pre-operative MVAC therapy appeared to extend median survival time (46 months vs. 77 months;  $p=0.06$ ).<sup>28</sup> Advantageous outcomes were strongly associated with clear cystoscopy specimens in both treatment and control groups – of those with pT0 at the time of radical cystectomy, 85% were alive at five years. Pathological complete response was in the region of 38% for MVAC candidates – compared to just 15% in the surgery alone control arm – strengthening the causal link between chemotherapy and improved survival.

Two consecutive trials from the Nordic Urothelial Cancer Group further validate pre-operative chemotherapy.<sup>29</sup> Five-year survival in the treatment arm increased from 48% to 56%, corresponding to an absolute risk reduction of 8% and a beneficial HR of 0.80. However, subgroup analysis of patients according to T stage, gender or age revealed no significant differences, thus making it impossible to select which patients are most likely to benefit. However, as these studies tended to recruit younger patients with good renal function and better cancer performance status, their conclusions require rigorous scrutiny.

Overall, the data substantiate a direct link between platinum-based combination neoadjuvant chemotherapy and improved survival measures. Several meta-analyses have since been published, all of which support a modest – but significant – effect. For example, retrospective analysis of 2688 patients collated from 10 studies generated a favourable HR of 0.87 ( $p=0.016$ ), regardless of the local therapy employed.<sup>30</sup> This translates into a survival advantage of approximately 5% at five years, a figure that has since been repeated in a larger meta-analysis.<sup>31</sup> In this second report, all but 196 of the 3005 patients included received cisplatin, with a 9% improvement in five-year disease free survival. Although the former study includes results from unpublished trials (perhaps undermining the reliability of the dataset used) and both analyses freely aggregate data from various clinical trials with heterogeneous combination cisplatin-based regimens, neoadjuvant chemotherapy appears to be largely beneficial.

But platinum-based chemotherapeutics are not without potential toxicity; indeed, single agent cisplatin has been associated with worse outcomes than surgery alone.<sup>30</sup> However, a systematic review of neoadjuvant MVAC chemotherapy only attributes 1.1% of deaths to this platinum-containing regimen.<sup>32</sup> Equally, evidence from the metastatic setting has shown that GC (gemcitabine and cisplatin) can produce similar response rates at reduced toxicity and, as such, may be of use pre-operatively.<sup>33</sup>

Several small non-randomised studies have lent support to the use of GC. For example, one phase II trial of 22 pre-cystectomy patients found a combined partial and complete radiographic response in 70% of muscle invasive TCCs treated with GC.<sup>34</sup> Of the 15 individuals that went on to have surgery, pathological complete response was evident in 4 (26.7%) of specimens. Median survival was 36 months with no deaths attributed to chemotherapy. Similar results have been reported elsewhere.<sup>35</sup> Although these studies may reasonably reassure that GC may provide a practical alternative to MVAC, neo-GC has yet to be validated in prospective, randomised clinical trials.

Indeed, more recent studies have supported the use of pre-operative “accelerated” MVAC (under hematopoietic growth factor coverage) in muscle invasive disease.<sup>36</sup> This dose dense approach minimises the delay to definitive treatment imposed by more protracted, conventional MVAC or GC therapies and – at present – may be considered the optimal regimen for patients eligible for cisplatin-based chemotherapeutics. Patients deemed unsuitable for typical cisplatin regimens may either receive less intense doses in a modified schedule (with or without nephroprotection), or avoid cisplatin altogether. This is usually achieved by substituting carboplatin for cisplatin, although the efficacy of this alternative remains controversial.<sup>37</sup>

Overall neoadjuvant chemotherapy is associated with a slight survival advantage for muscle invasive bladder cancer. However, it does not allow for the selection of patients most likely to benefit and can only be systematically provided at the known risk of overtreatment. Metastatic disease shows chemoresistance in approximately 40-60% of cases and it is not unreasonable to assume that locally advanced TCC will show similar rates of non-responsiveness. Therefore, neo-chemotherapy may be considered as a standard of care, although clinicians and patients should still be able to elect for definitive local therapy with the option of post-operative chemotherapy.<sup>18</sup>

### **Adjuvant chemotherapy**

As in neo-chemotherapy, the principle of adjuvant drug administration is to eliminate occult metastases beyond the margins of local therapy. It provides two further key theoretical benefits: firstly, definitive treatment is not delayed and, secondly, therapy type can be based upon defined pathological criteria. The ability to risk stratify is key, as those most likely to benefit appear to be those at greatest risk of relapse.<sup>38</sup> Indeed, adjuvant chemotherapy may be especially indicated in certain high-risk patient groups, including those demonstrating residual node and margin positive disease.

One obvious issue with adjuvant approaches is whether patients are sufficiently fit following surgery. Two different studies report post-cystectomy complications in 30-58% of cases, potentially delaying the timely administration of systemic therapy.<sup>39,40</sup>

Several trials have examined the role of adjuvant chemotherapy in muscle invasive disease, producing mixed results. One early trial suggested that post-operative chemotherapeutics were associated with improved time to progression, cancer regression and overall survival parameters within three years; yet the same trends were not seen at five years.<sup>41</sup> This was, however, only a small study of 91 patients, further confounded by non-standard chemotherapy regimens and poor application of treatment (fully a quarter of those randomised to the treatment group never received chemotherapy).<sup>41</sup> Similar issues were encountered in two further trials, both of which were abandoned after inadequate accrual.<sup>42,43</sup> Although these

studies also demonstrated advantageous progression free survival outcomes (HRs of 2.84 and 2.84, respectively), the results are based upon <100 patients. Ethically too, these studies have been criticised – primarily for failing to treat those in the observation-only group undergoing relapse. Long-term follow-up has addressed these concerns and (with a further 117 patients added to the dataset) continue to demonstrate a marked benefit to adjuvant therapy.

A meta-analysis of six such RCTs collated results from 491 patients, revealing an absolute survival improvement of 9% at three years (HR 0.75;  $p=0.019$ ).<sup>44</sup> Although these data demonstrate the feasibility and safety of adjuvant drug administration, underpowering and inconsistent methodologies prevent the authors from recommending this type of chemotherapy as standard.

Another issue is that many early studies were closed after interim analysis. For example, the EORTC 30994 phase III trial has yet to publish its results (although it too was terminated after poor accrual). Interestingly, this study design permitted the use of MVAC or GC chemotherapy, at the physician's discretion. Recent research has suggested no statistically significant benefit to GC over observation in the adjuvant setting.<sup>45</sup> However, with only 194 patients recruited, even this multicentre trial was underpowered to show the impact of treatment on any endpoint assessed.

There appears to be no compelling role for non-platinum based chemotherapy post-operatively. Gemcitabine alone in patients deemed unsuitable for cisplatin therapy produced a trend towards improved survival and disease-free progression when compared to surveillance alone, but neither outcome measure reached significant thresholds in a recent trial.<sup>46</sup> Similarly, single-agent cisplatin has yet to be validated post-operatively. For example, one small prospective study failed to detect a survival advantage at five years when compared to expectant observation.<sup>47</sup>

Overall, there appears to be low quality evidence to support the utility of adjuvant chemotherapy for locally advanced disease.<sup>48</sup> Therefore, patients with high-risk cancer and/or pathological node involvement who fulfill fitness criteria (and who are willing to accept known toxicity risks without proven survival benefit) might be considered candidates for post-operative treatment. Yet a recent systematic review failed to demonstrate improved survival outcomes – even in selected subgroups with extravesical malignancy.<sup>49</sup>

Identifying those individuals deemed 'high-risk' therefore presents particular challenge. One novel idea revolves around selection by p53 status (with several retrospective studies suggesting that p53 changes may be prognostic for TCC recurrence and adjuvant MVAC efficacy). Immunohistochemistry for p53 expression segregated one study population into two groups, either managed conservatively or with three cycles of chemotherapy.<sup>50</sup> Although the authors note a high-rate of non-compliance with the original study design, p53 status appeared to have no meaningful effect on endpoint outcomes.

### Radiotherapy

The potential advantages of radical radiotherapy as definitive treatment include bladder preservation, avoidance of surgery and intact sexual function. Observational studies suggest that this modality provides five-year survival rates in the region of 28-50%, with successful salvage cystectomy in ~20% of failed cases.<sup>51,52</sup> Although direct comparison with radical cystectomy is challenging, large surgical and radiotherapy series report similar long-term survival outcomes.<sup>53</sup>

The marginal superiority of scheduled surgery is supported by two meta-analyses. In the first, three RCTs demonstrate a five-year survival benefit to pre-operative radiotherapy and planned cystectomy over radical radiotherapy with secondary salvage cystectomy.<sup>54</sup> A second Cochrane review corroborates these data, although the calculated odds ratio of 0.71 was sufficient only to suggest a trend rather than significance.<sup>55</sup> However, the advancing age of these particular studies questions whether their findings can be applied to more modern techniques.

No RCTs directly compare radiotherapy to chemotherapy as single modalities in bladder cancer. However, one early phase II study demonstrated a modest advantage to chemoradiotherapy over radiotherapy alone, both in terms of ten-year survival and bladder preservation rates.<sup>56</sup> Should patients prefer radical radiotherapy with the intention of bladder sparing, it is important that they appreciate an increased risk of complications during salvage cystectomy. For example, one small study of 23 patients reported higher complication rates in those with a history of external beam irradiation versus a control matched planned-cystectomy group (48% vs. 26%;  $p<0.045$ ).<sup>57</sup> Thus, cystectomy after failed radiotherapy comes with a recognized morbidity risk.

As in chemotherapeutic approaches, it would be of value to be able to identify those patients most likely to benefit in advance. One retrospective analysis of 342 patients with a median 7.9-year follow-up highlighted tumour multiplicity ( $p<0.001$ ), ureteric obstruction ( $p=0.001$ ) and higher T stage ( $p=0.004$ ) as independent prognostic factors in relapse rates.<sup>58</sup> Those patients with these features might be better discouraged from radical radiotherapy, whereas younger patients with high-grade exophytic tumours appear most likely to respond.

Further research might aim to advance our understanding of these predictive markers, or investigate optimal dose, fractionation and scheduling considerations in treating locally invasive disease. Although a recent phase III trial (BC2001) assessing the viability of reduced high-dose volume radiation therapy failed to formally demonstrate noninferiority of locoregional control and a reduced side effect profile, additional studies in this area are required. For example, the theory that 'accelerated radiotherapy' minimises repopulation by surviving clonogens has yet to be rigorously tested.<sup>59</sup>

If radiotherapy is to be delivered with curative intent, the European Society for Medical Oncology (ESMO) advises that external beam radiotherapy should be delivered with 3D conformal or intensity-modulated techniques, ideally under image guidance.<sup>18</sup> Typically, this would be provided in conjunction with a multimodal bladder-preserving approach.

### Synchronous Chemoradiotherapy: Bladder Preservation

Radiotherapy alone is a recognized bladder-sparing alternative to cystectomy in patients with muscle-invasive disease, yet it remains associated with a relatively high rate of incomplete response or local recurrence. Synchronous chemoradiotherapy may therefore have advantages over radiotherapy alone and may be especially useful in the treatment of those patients unfit for major surgery. This is supported by evidence from other primary cancer sites, including cervical and anal malignancies.<sup>60,61</sup>

A recent multicentre phase III trial demonstrated that that concomitant chemotherapy (with fluorouracil and mitomycin C) and radiotherapy significantly improved locoregional control of muscle-invasive disease when compared with radiotherapy alone.<sup>62</sup> The

addition of chemotherapy to standard-dose radiotherapy was associated with a relative reduction of 33% in the risk of locoregional recurrence and almost 50% in invasive recurrence. Improved locoregional control was achieved with only modest increases in toxic effects that did not achieve statistical significance with respect to grade 3 or 4 outcomes. Long-term follow up revealed a clear advantage for those patients randomised to the chemoradiotherapy group: at 5 years, overall survival rates were 48% in the experimental arm versus 35% for those receiving radiotherapy alone. This was achieved without increased rates of salvage cystectomy. Further research might seek to establish whether synchronous chemoradiotherapy is preferable to radical cystectomy as definitive treatment.

This study also contributes two further important observations. Firstly, that the benefits of synchronous chemoradiotherapy were independent of a history of neoadjuvant chemotherapy – suggesting that neoadjuvant and concomitant chemotherapy confer separate benefits on distant and local control, respectively. Secondly, fluorouracil and mitomycin C in combination are effective radiosensitising agents and may be considered for patients unfit for cisplatin-based therapies. This adds to previously proposed alternatives to radiosensitisation based on tumour hypoxia, typically induced by the use of nicotinamide and carbogen.<sup>63</sup> Together, these trials suggest that it may be time to re-evaluate the preference for surgery over bladder-sparing options, particularly in those patients at high-risk for surgical complications.

#### Trimodal Therapy: Bladder Preservation

Trimodality treatment – i.e. combining chemoradiotherapy with bladder-sparing surgical options – may also represent a viable alternative to radical cystectomy in muscle-invasive bladder cancer. For example, two prospective studies in which chemoradiotherapy was augmented by transurethral resection demonstrated that this approach could be safely applied in selected patients.<sup>64,65</sup> Accurately identifying those individuals most likely to benefit may well be difficult, although tumour grade and status after the initial resection appear to be important prognostic factors.<sup>65</sup>

Bladder-preserving multimodal approaches demand a high level of multidisciplinary cooperation and patient compliance. Meticulous long-term surveillance is required to detect intravesical tumour recurrences and this should be considered when offering bladder-sparing options. This decision may be further informed by several clinical criteria, including: early tumour stage, a visibly complete or maximally debulking TURBT, absence of associated carcinoma in situ (CIS) and adequate bladder capacity and function.<sup>66</sup> If persistent or recurrent disease is identified during response evaluation or follow-up, prompt salvage cystectomy is required.

## Discussion

Even with accurate staging information, the appropriateness of

various different management options remains contentious. For example, the National Comprehensive Cancer Network (NCCN) and NHS guidelines detail at least four separate care plans for the treatment of primary cT2 disease, summarized in **Table 2**.<sup>67</sup> This highlights the need for individually tailored therapy, with consideration given to factors such as age and comorbidity, as well as patient preference. In the absence of convincing evidence to support one approach over another, it is perhaps this last component that primarily directs therapeutic strategy.

NCCN and ESMO guidelines both advocate radical cystectomy with extended lymphadenectomy as the standard treatment for muscle invasive bladder cancer without nodal involvement.<sup>18,68</sup> Those patients with a good performance status and intact organ function should be strongly considered for neoadjuvant cisplatin-based combination chemotherapy, whereas those unfit for surgery should be considered for radiotherapy either with or without chemotherapy. A small minority of patients (<5%) with a solitary T2 lesion in a suitable location without concurrent CIS may be eligible for partial cystectomy, usually in conjunction with neoadjuvant chemotherapy. Partial cystectomy is not an option for patients with T3 disease or above.

In both post-cystectomy patients and those pursuing bladder-sparing options, follow-up is an essential component of long-term management, although protocols vary worldwide.<sup>18,68</sup> As a minimum, urine cytology and imaging of the chest, abdomen and pelvis should be performed every 3 to 6 months for 2 years and then as clinically indicated. Routine bloods include creatinine, electrolytes and liver function tests. Urethral wash cytology is recommended if urethrectomy has not been carried out and/or there is a history of CIS.

Follow-up of patients opting for partial cystectomy or other bladder-sparing approaches is the same as for radical cystectomy, except that these individuals require additional 3-monthly surveillance by cystoscopy (usually with selected mapping biopsies) for the first 2 years at least. Continued monitoring for recurrence is especially important, as most are superficial and therefore readily amenable to endoscopic treatment.

## Conclusion

The management of muscle invasive bladder cancer remains controversial. The advent of better profiling methods using high throughput technologies might aid in staging, prognosis and selection of optimal treatment approaches;<sup>69-71</sup> until then, management pathways are guided by an often inconsistent and unclear literature base. However, the value of reliable research is as much in guiding the patient as the clinician. Protocols for invasive urothelial cancers incur known morbidity and mortality risks and, ultimately, informed patients must be involved in the decision-making process.

**Table 2.** Summary of Primary Care Protocols for cT2 Disease.

Treatment Option	Notes
Radical cystectomy with urinary diversion	Strongly consider neoadjuvant cisplatin-based combination chemotherapy
Segmental/partial cystectomy	Consider neoadjuvant cisplatin-based combination chemotherapy
Selective bladder sparing following maximal TURBT	Consider concurrent radiotherapy and chemotherapy ± salvage cystectomy
TURBT alone	Extensive comorbidities/poor performance status
or radiotherapy alone	
or chemotherapy alone	



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#### Acknowledgments

None.

#### Conflict of Interest Statement & Funding

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

#### Author Contributions

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

#### Cite as:

Luck J. Role of Chemotherapy and Radiotherapy in the Surgical Management of Muscle Invasive Bladder Cancer. *Int J Med Students*. 2014 Jul-Oct;2(3):125-31.

# Two Cases of CrossFit®-Induced Rhabdomyolysis: A Rising Concern

Madhur Rath<sup>1</sup>.

## Abstract

**Background:** The author reports the cases of two adult males who presented with severe rhabdomyolysis following identical CrossFit® workouts performed on the same day, at the same time and at the same location. **Results:** For both cases, symptoms of rhabdomyolysis disappeared upon discontinuation of the regime and within three days of aggressive hydration and rest. Patients made a complete recovery upon discharge. **Conclusion:** The rhabdomyolysis was attributed to the same excruciating workout both men underwent. Exertional rhabdomyolysis exemplified by the cases presented highlights a rising concern over the health consequences of the popular training program. CrossFit®-induced rhabdomyolysis is underrecognized and should be considered in patients presenting with signs and symptoms of rhabdomyolysis.

**Keywords:** Exercise, Rhabdomyolysis, Supplements, Dehydration, Sport (Source: MeSH, NLM).

## Introduction

Extensive information has been published about rhabdomyolysis caused by high-intensity CrossFit® training regimes, and yet the diagnosis of CrossFit®-induced rhabdomyolysis remains underrecognized in the emergency department.<sup>1</sup> In rhabdomyolysis, contents of injured muscle cells leak into the circulation, resulting in electrolyte abnormalities, hypovolemia, acidosis and acute renal failure.<sup>1</sup> An increase in free intracellular calcium triggers activation of proteases, increased skeletal muscle cell contractility, mitochondrial dysfunction, and the production of reactive oxygen species, resulting in skeletal muscle death. The association between rhabdomyolysis and triggering events such as the intense CrossFit® workout regimes (the equivalent to a high intensity military workout) was first explored by Greg Glassman in 2005 in a case series out of Santa Cruz, California.<sup>1</sup> Since then, this prevalent condition has surfaced across the United States with a plethora of etiologies.

## The Cases

A 33-year-old male presented to the Dekalb Medical Center Emergency Department in Atlanta, Georgia for complaints of muscle pain, soreness and stiffness in his biceps and across his chest ongoing after a CrossFit® workout that he had three days prior involving 100 plus push-ups, pull-ups, squats and sit-ups all in the span of thirty minutes. Patient also had some diarrhea with very dark colored urine and reported feeling nauseous but denied vomiting. He had been taking Atorvastatin 40 mg daily for hypercholesterolemia. Physical examination revealed a pulse rate of 114 beats/minute and a blood pressure of 137/86 mmHg. The remainder of the examination was unremarkable. His complete blood count and comprehensive metabolic

### Key Points:

- Although the causal link between rhabdomyolysis and intense workout regimens has been well documented, exercise-induced (exertional) rhabdomyolysis generally go unreported as very few cases are fatal and most resolve with adequate treatment.
- The use of supplements among those undergoing CrossFit® training may increase their vulnerability to skeletal muscle breakdown and obscure the diagnosis of rhabdomyolysis.

lic panel were unremarkable. Urinalysis was positive for trace amounts of blood. In addition, patient's creatine kinase (CK) level was severely elevated at 98,559 U/L on admission (normal range 52-336 U/L), and abdominal ultrasound was unremarkable. The emergency department physician clinically made the diagnosis of rhabdomyolysis without any further testing.

The second case is of a 37-year-old male presented to Dekalb Medical Center Emergency Department immediately following the above mentioned patient who also complained of upper extremity pain after undergoing the same CrossFit® workout at the same gym and at the same time three days prior to admission. Patient had very dark colored urine and abdominal pain, but denied nausea and vomiting. He had been taking Colonix® and Toxinout®, two weight supplements as part of his workout regime. Physical examination revealed a pulse rate of 51 beats/minute and, blood pressure was 120/57 mmHg. His complete blood count was unremarkable and comprehensive metabolic panel showed elevated aspartate transaminase at 1997 U/L and alanine transaminase at 638 U/L. Urinalysis was positive for trace amounts of blood. The patient's CK level was 148,182 U/L on admission (normal range 52-336 U/L) and an abdominal ultrasound was benign. The attending physician made the diagnosis of rhabdomyolysis. Both patients were treated

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Submission: Apr 28, 2014  
Acceptance: Oct 13, 2014  
Process: Peer-reviewed

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with IV fluids (Ringer's lactate). All forms of exercise as well as supplements were terminated until they were discharged.

## Discussion

There are two proposed potential reasons that may contribute towards emergency medicine physicians being reluctant to conclude CrossFit® as the precise etiology of a patient's rhabdomyolysis.

*Firstly, it is an underreported diagnosis:* Avid proponents of the CrossFit® workout regimen maintain that musculoskeletal deterioration occurs when athletes over-exert themselves, not just when performing an inordinate amount of repetitions at oftentimes unaccustomed weight levels for above-normal periods of time – the standard protocols for CrossFit®. The demanding nature of the workout has led to its adoption by Canadian Forces, U.S. Army Commands and U.S. Marine Corps. Published records have shown exertional rhabdomyolysis in military training rising in epidemic proportions at 166% per year.<sup>2</sup> However, statistics suggesting a correlation between workouts at CrossFit® locations and cases of rhabdomyolysis have yet to be published. Furthermore, case fatality rates are less than 5% from exertional rhabdomyolysis and most otherwise healthy individuals recover rather quickly with aggressive hydration and management.<sup>3</sup> Hence, metabolic, renal and systemic complications are avoided and a significant number of cases might go unidentified.

*Secondly, it is a confounding diagnosis:* Skeletal muscle breakdown as a side effect of the administration of statins, such as atorvastatin, is an issue of intense interest that has been well-documented. In fact, in a 2010 study by Guis et al, elevation of creatine kinase occurs in 3-5% of medication-induced cases, while significant rhabdomyolysis surfaces in 0.04-0.20%

of them.<sup>4</sup> As a result of the sheer intensity of the workouts, a number of nutritional supplements are popular among CrossFit® athletes to facilitate the training and recuperation phases of the exercise routine and have been heavily publicized in gymnasiums across the nation. Certain products, such as Creatine®, have well-known side effects of muscle cramping, straining and dehydration, all of which can contribute to the rupturing of skeletal muscles.<sup>5</sup> Colonix® utilizes a laxative tea and requires at least 64 oz. of liquid with use. It is contraindicated in patients with dysphagia. Additionally, vomiting, diarrhea and excessive dehydration are all potential adverse effects.<sup>6</sup> Furthermore, its active ingredient, psyllium, functions as a non-systemic cholesterol-lowering agent, just like statins. Dehydration and choking are frequent unfavorable side effects if psyllium is taken without adequate water as it thickens secretions in the throat.<sup>7</sup> Toxinout®, a complex of herbs, amino acids, vitamins and antioxidants, is contraindicated in renal disease – what skeletal muscle rupture could lead to if not treated immediately. Both aforementioned supplements are hence capable of exacerbating rhabdomyolysis and its lethal complications.<sup>8</sup>

## Conclusion

CrossFit® began as an exercise regimen in 2005 with just 10 locations in the United States. Currently, there are over 15,000 locations that offer CrossFit® training across North America, and the number is growing.<sup>8</sup> The workout regime itself, the publicity surrounding its advocates, and the widespread use of products marketed at the CrossFit® locales make it increasingly crucial that emergency room physicians consider CrossFit®-induced rhabdomyolysis in their differential diagnoses when they encounter a case with typical signs and symptoms in the context of a patient who undergoes CrossFit® training.



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## Acknowledgments

None.

## Conflict of Interest Statement & Funding

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

## Author Contributions

Conception and design the work/idea, Collect data/obtaining results, Analysis and interpretation of data, Write the manuscript: MR.

## Cite as:

Rathi M. Two Cases of CrossFit®-Induced Rhabdomyolysis: A Rising Concern. *Int J Med Students.* 2014 Jul-Oct;2(3):132-4.

# High Alert For Cannabinoid Hyperemesis Syndrome: A Case Report

Madhur Rath, <sup>1</sup>

## Abstract

**Background:** A 32-year-old Caucasian man presented with intractable nausea, psychogenic vomiting, abdominal pain and compulsive hot-water bathing behaviors following the habitual use of cannabis for years, consistent with the uncommon and frequently overlooked diagnosis of Cannabinoid Hyperemesis Syndrome. This was his third admission to the emergency department with the same complaints and symptoms which had persisted for over two years without a recognizable etiology. All imaging studies done on each visit were unremarkable. **Results:** The patient was clinically symptomatic with the aforementioned presenting complaints, but disappeared upon discontinuation of the cannabis. Within two days of supportive treatment in addition to temporary relief of symptoms with bathing. To date, no effective cure has been sought for this unique diagnosis other than abstaining from cannabis use. **Conclusion:** A complete recovery was made three days following admission. The presenting symptoms were attributed to the smoking behaviors. The patient was followed up by his primary care physician once released from the hospital. A very rare diagnosis surfaced a number of times with the same patient in the same setting over the span of a couple years, but was overlooked due to its rarity. Hence, physicians should list it higher on their differentials when dealing with a patient with a history of drug abuse.

**Keywords:** Cannabinoids, Vomiting, Baths, Compulsive Behavior (Source: MeSH, NLM).

## Introduction

Cannabinoid Hyperemesis Syndrome (CHS) was first noted by Allen JH, and De Moore GM, when they explored the association between chronic cannabis abuse and a cyclical vomiting illness that presented in a series of cases in South Australia in 2004.<sup>1</sup> It is a syndrome characterized by the chronic use of cannabis, recurrent episodes of severe nausea, vomiting, abdominal pain, and habitual bathing behaviors to help resolve symptoms (a pathognomonic feature). The mechanisms explaining the adverse consequences of long-term cannabis toxicity remain largely unknown, however various pathogenic mechanistic theories maintain that several peripheral CB<sub>1</sub> cannabinoid receptors in the brain are responsible for the presenting signs and symptoms.<sup>1</sup> Almost a decade has passed since the first published case of CHS and yet in the emergency department, this peculiar disease remains obscure and under diagnosed. In fact, before a case series published by Simonetto et al., at the Mayo Clinic in 2012 recognizing 98 patients afflicted with the syndrome, only 33 cases of CHS was published.<sup>2</sup> Since the first aforementioned documentation and with the recent legalization of medical marijuana in numerous states, the syndrome has now surfaced across North America, Western Europe and Australia.<sup>3</sup>

## The Case

A 32 year old male presented to the Dekalb Medical Center Emergency Department in Atlanta, Georgia for nausea, non-bloody vomiting, and diffuse colicky abdominal pain over the course of a week. Food intake exacerbated his condition and

### Key Points:

- The low number of reported cases despite the pathognomonic features of the syndrome render CHS rather difficult to diagnose clinically.
- As cannabinoids are supposed antiemetics, their habitual use leading to vomiting as one of the more potent side effects is a conundrum.
- The ironic nature of the syndrome has led to theories being proposed regarding its mechanism, but none of the hypotheses have been confirmed to date.

his nausea was relieved by taking hot showers. Patient admitted to smoking half a pack of cigarettes per day as well as smoking up to five blunts of cannabis a day for the past six years. The rest of the review of systems was noncontributory. On physical examination, his blood pressure was 140/90, his pulse rate was 104/min and his mucous membranes were dry. The remainder of the physical examination, his complete blood count, comprehensive metabolic panel and arterial blood gas were all unremarkable. Serum amylase and lipase levels were within therapeutic range. His urine drug screen was positive for tetrahydrocannabinol (THC). It was later noted that these symptoms had persisted for over 2 years and the patient had been admitted with the same complaints three times to the same emergency department. Each time, abdominal X-Rays, CT scans, ultrasounds, esophagogastroduodenoscopies, colonoscopies, and stool studies were performed and were all unremarkable. No previous interventions were noted on each visit. In his third and final admission, the clinical diagnosis of CHS was made. Treatment was supportive with fluid hydration and rest. The patient abstained from cannabis use for the duration of his stay in the hospital until discharge three days later.

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Submission: May 6, 2014  
Acceptance: Oct 13, 2014  
Process: Peer-reviewed

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## Discussion

It has been noted that it takes up to an average of seven visits before patients with chronic vomiting are diagnosed with any underlying cause.<sup>4</sup> In fact, in a survey conducted by Venkatesan T, et al., revealed that 89% of the patients with chronic vomiting were not diagnosed in the emergency department.<sup>3</sup> Emergency medicine physicians may be hesitant to place the diagnosis of CHS high on their differentials for the following reasons:

CHS is a rare diagnosis: As mentioned previously, up until two years ago, few cases had been published for CHS.<sup>2</sup> Although this low number suggests that the diagnosis is uncommon, medical professionals and cannabis users may not be conscious of the diagnostic symptoms. Consequently, a significant number of cases might be unrecognized. Here a case of cannabis use was described where the patient presented multiple times with the same complaints and an exhaustive medical evaluation failed to reveal another etiology. Several common differentials for nausea and vomiting were considered including overdoses of alcohol or medications, bacterial and viral infections, inflammatory gastrointestinal diseases, and central nervous system or psychiatric conditions. However, no evidence supported any of the aforementioned causes.

CHS is a paradoxical diagnosis: Cannabinoids are medically used antiemetics for the prevention of nausea and vomiting caused by chemotherapy via a mechanism inhibiting the release of emetic neurotransmitters by stimulating presynaptic cannabinoid CB<sub>1</sub> receptors.<sup>5</sup> Hence, cannabinoids inducing hyperemesis appears to be contradictory and the pathophysiological mechanism(s) underlying the induced vomiting is still unknown, therefore obscuring the role of cannabinoid in patients with hyperemesis.

CHS is an under-researched diagnosis: The pathognomonic feature of CHS of compulsive warm water bathing for temporary relief of symptoms has no definite explanation. The CB<sub>1</sub> receptor is near the thermoregulatory center of the hypothalamus and chronic stimulation may be counteracted with warm showers, but to date, this theory has yet to be verified.<sup>6</sup> Alter-

nate explanations theorize that CB<sub>1</sub> receptor-mediated vasodilation of the gut with chronic cannabis use may contribute to the symptoms. A redistribution of blood flow from the gut to the skin with hot water could bring relief to the patient in a “cutaneous steal syndrome” pattern.<sup>2</sup>

The aforementioned case series published in 2012 by Simonetto et al., identified 98 patients who met inclusion criteria for diagnosis – recurrent vomiting with no other explanation for symptoms, cannabis use preceding symptom onset and absence of major illness that could explain the symptoms. To further refine the decisive factors, the authors have now expanded the flow chart to include relief of symptoms with hot showers or baths, resolution with cannabis cessation, several cycles of nausea and vomiting, abdominal, epigastric or periumbilical pain, weekly use of marijuana, age under 50, weight loss greater than 5 kg, normal bowel habits, negative laboratory, radiographic, and endoscopic test results with a morning predominance of presenting symptoms.<sup>2</sup> These can all further aid ED physicians in formulating their differentials when confronted with patients who present with similar symptoms to rule out differentials such as gastroesophageal reflux disease, peptic ulcer disease, inflammatory bowel disease, appendicitis and pancreatitis among other gastrointestinal diseases high on the possible diagnoses without colonoscopies, endoscopies, esophagogastroduodenoscopies and imaging studies to aid them. Still, studies with lower attrition rates are needed and validation of the proposed diagnostic criteria is required.

## Conclusion

The use of cannabis has become more prominent and it is slowly gaining notoriety as one of the most commonly abused drugs worldwide. In fact, an estimated 2.6 million individuals in the USA become new users every year.<sup>7</sup> Though further studies are warranted to further understand the prevalence and symptoms of this uncommon disease, CHS should be considered higher on the differential list when patients present with chronic vomiting with no underlying etiology given the widespread and continuously rising use of cannabis today. With an accurate history and knowledge of this phenomenon, expensive and invasive diagnostic treatment can be avoided.

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## Acknowledgments

None.

## Conflict of Interest Statement & Funding

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

## Author Contributions

Conception and design the work/idea, Collect data/obtaining results, Analysis and interpretation of data, Write the manuscript: MR.

## Cite as:

Rathi M. High Alert For Cannabinoid Hyperemesis Syndrome: A Case Report. *Int J Med Students*. 2014 Jul-Oct;2(3):135-7.



# The Silent Suffering of Jane Doe: Negligence of Mental Health Problems in Daily Practice

Julius Kremling.<sup>1</sup>

*About the Author: Julius Kremling is a fourth year medical student who has studied in Germany, Ireland and Belgium.*

## The Experience

In a vast number of different specialities and in primary care during placements, I have encountered many different diseases, patients and doctors. But one seems to be a constant visitor: Jane Doe. Jane Doe is no real patient but a synthesis of many I have seen in this form very often and who shows some distinct features that distinguishes her from other patients. It might be her first visit to this service or a review appointment, however, whatever it is, lots of investigations have been done or will be undertaken. When she enters the room the doctor focuses on her (physical) symptoms and signs, takes her history and examines her. While doing so, she usually breaks into tears repeatedly and mentions troubles in college or at her workplace, anorexia, insomnia, financial difficulties... the list seems to be endless. The attending doctor, however, only offers a few kind words and ignores the emotional and mental breakdown of the patient. Later, when the consultant reviews the patient, the whole lot repeats itself and again the mental status of the patient is ignored. She is reassured that she will be well looked after and receives a review appointment and maybe even a specialist consult. Her urgent need for psychotherapy or any kind of psycho-social support, however, is once again ignored.

I have chosen her name deliberately since we all know the unknown corpse that appears frequently on television. A corpse, not a human being, missed by nobody that only gets the attention it deserves once dead. Though this patient showed several features of depression, her presenting complaint was reduced to a pure physical problem while her chief complaint was ignored. Considering that, according to the Global Burden of Disease 2010 study, depressive disorders are a leading cause of global burden of disease, such behaviour on the part of doctors shows ignorance of patients' needs and negligence of medical duties.<sup>1</sup> But it is not only failure of the attending physicians but failure of the medical profession itself. The junior doctor who took the history and examined the patient first, the consultant who reviewed the patient, the nurses who took her vitals and showed her to the examination room and last but not least myself as a medical student who failed to bring up her obvious worries.

Psychiatric diseases often go untreated, not to speak of all those little ailments that have not made it into the latest Diagnostic and Statistical Manual of Mental Disorders which, however, still bother many of us.<sup>2-5</sup> Taking a psychiatric history outside a psychiatric ward or clinic feels to be much more intrusive than any physical examination. It is something people want to speak about only behind closed doors. We - that includes both already practising doctors and medical students - often feel embarrassed by the mere thought of asking our patients about some "strange" thoughts, ticks and emotions. Are we trying to conceal our own inner turmoil?

In our society crazy is not cool. It is stupid. It is antisocial. It is dangerous. It is something we laugh about and something we definitely do not want to be.<sup>6,7</sup> When I wander through the corridors of any hospital I usually pick up easily many anecdotes, rumours and jokes made at the expense of everybody with a mental health problem. I frequently catch myself drifting into the same discriminatory pattern of thinking many doctors and fellow students have. Stigmatisation seems to be omnipresent and contagious. I often sense that making some negative comments on people with mental health problems is thought to be good form on the wards. However, such behaviour of medical staff can only discourage patients with mental health problems to seek professional help and we have to ask ourselves if denying help to some of society's most fragile members is what we want.<sup>7,8</sup> I only wrote about Jane, but beware that John is her brother and though mental disorders are still commonly regarded as a "women's thing", he might also be troubled.<sup>9</sup>

Submission: May 9, 2014  
Acceptance: Jun 28, 2014

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## Acknowledgments

None.

## Conflict of Interest Statement & Funding

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

## Author Contributions

Write the manuscript: JK

## Cite as:

Kremling J. The Silent Suffering of Jane Doe: Negligence of Mental Health Problems in Daily Practice. *Int J Med Students.* 2014 Jul-Oct;2(3):138-9.

# Cross-Cultural Training: The Importance of Volunteering Abroad in Medical School

Nidhi Ravishankar.<sup>1</sup>

**About the Author:** Nidhi Ravishankar is entering second year medical school at the Windsor University School of Medicine.

## The Experience

Volunteering overseas whilst in medical school has proved extremely beneficial not only for my academic growth, but also for professional and personal growth.

There is a marked disparity between what is taught in medical schools and what is expected of physicians in practical aspects.<sup>1</sup> In most medical schools, medical students acquire their training and skills in large tertiary care hospitals, where the focus is placed on making the right diagnosis. This takes precedence over the interpersonal communication between the health-care practitioner and the patient. I was able to learn such skills through direct contact with the patients, as well as medical skills such as taking blood pressure, blood glucose levels, patient history, neurological examination and basic physical examination.

During my time in St. Kitts, I volunteered with a group called "Students For Health (SFH)" - a student-run volunteering clinic offering free health-checks to the local community. This community initiative was bolstered by Dr. Vishal Surender of Windsor University School of Medicine who oversees the entire group.

As a volunteer for SFH, I was able to comprehend the huge difference between the standards of medical practice in the developed and developing worlds. As told by the locals who attended the clinic, the major hospital on the island, Joseph N. Frances General Hospital, dealt mainly with immediate and minor cases and patients were seen in order of severity. As a result, frequent health checkups were left to be conducted in community clinics which were often said to be "crowded". SFH therefore proved to be a helpful alternative for the community to acquire health-checkups without having a long wait.

During my first semester of medical school, there was very little time to learn clinical skills effectively such as taking blood pressure, using a stethoscope, taking blood glucose etc. because of the rapid pace of the subjects. SFH allowed me to build these skills through rigorous training and an examination, and implement them on patients. The training allowed me to gain

**Figure 1.** Consulting on the Treatment Regimen for a Patient's Hypertension.



confidence in my clinical knowledge so that my clinical years can be more productive and enjoyable.

When I went onto the field and became part of a team who offered the health checkups every week, I came in contact with patients who had illnesses and conditions that I rarely saw in the developed world. Patients came in with Marfan syndrome, Paget's disease and other conditions that I had only learned in class. It was an extremely meaningful experience to observe and interact with patients with these conditions. I was able to learn about them through a more personal approach, rather than just an academic one.

In addition, SFH also offered me the opportunity to model professionalism as well as ethical and culturally sensitive treatment of patients. As a student from Toronto, Ontario, one of the biggest and most multicultural cities in Canada, I was experienced in communicating with patients from various backgrounds, but my time in St. Kitts proved that I had a lot more to learn. Although advanced technology or a more pleasant environment may be conducive to better-quality care, the evidence indicates only a weak link between such structural elements and better health outcomes.<sup>2</sup> This was especially evident when we had

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Acceptance: Jul 26, 2014

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many tourists visiting our clinic indicating that they had rarely seen freeclinics being offered in their respective countries. Most of these foreign patients were well-versed in medicine, however it was surprising to see that one of them was unaware of his hypercholesterolemia. Although there are many benefits to being served medically in developed countries like Canada and the United States, the patient doctor relationship is very minimal due to the high volume of patients. They were very receptive to the clinic because they appreciated the personal depth that came with the visit.

As a health-care provider, we are expected to approach cross-cultural education that can be used to care for any patient, anytime, anywhere. Although a purely algorithmic approach is being taught in medical schools, the best kind of learning comes from interacting with various patients where we can at least have a framework to care for patients regardless of race, ethnicity or cultural background.

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### Acknowledgments

I would like to acknowledge the Students for Health team at Windsor University School of Medicine at St. Kitts.

### Conflict of Interest Statement & Funding

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

### Author Contributions

Write the manuscript: NR

### Cite as:

Ravishankar N. Cross Cultural Education: The Importance of Volunteering Abroad in Medical School. *Int J Med Students*. 2014 Jul-Oct;2(3):140-1.



## Massive Open Online Courses and Medical Education

### To the Editor,

A 2010 publication by the Carnegie Foundation, "Educating Physicians: A Call for Reform of Medical School and Residency," highlighted the current challenges facing medical education, including issues surrounding quality, costs and the ability to deliver medical education to enough students.<sup>1</sup> In order to address these challenges, innovative learning methods are needed, such as those offered by the wide availability of the internet. Over the last decade, there have been a number of advances in online education, including the emergence of massive open online courses (MOOCs). These courses aim to deliver high-quality education to large numbers of students around the world via the internet and at little or no cost. Although the term 'MOOC' was coined by Cormier and Alexander in 2008 in their comments on the 'Connectivism and Connective Knowledge' course delivered by Siemens and Downes, MOOCs did not gain traction until 2012, when Sebastian Thrun launched his startup Udacity.<sup>2</sup> Since then, many MOOC platforms have been launched, including Coursera, Edx, and FutureLearn, among others. These courses have gone viral, attracting many millions of students and a number of elite institutions from around the world. The latest Coursera infographic indicates that over five million students and over one hundred institutions have participated in over five hundred courses with hope to revolutionize online education (Available from: <http://blog.coursera.org/post/64907189712/a-triple-milestone-107-partners-532-courses-5-2>, updated 2013 Oct; cited 2014 July 27). In this letter, I discuss the current and future role of MOOCs in medical education shedding the lights on the challenges facing such role with some suggestions to improve this newly developed model.

The number of medical MOOCs is steadily increasing, with 73 courses offered in English by Coursera (Available from: <https://www.coursera.org>, updated 2014 Dec; cited 2014 July 27) and 19 courses by Edx (Available from: <https://www.edx.org>, updated 2014 Dec; cited 2014 July 27) in disciplines including genetics, physiology, pharmacology, and public health. The current format of these courses is formed mainly of three pillars; video lectures, exams and assignment and interaction forums. Discussions about the role of MOOCs in medical education between optimistic and skeptical are rapidly increasing. Regarding the points of optimism, these courses represent an excellent opportunity for medical students to learn new fields and topics (that may be not taught in medical school, such as bioinformatics and nanotechnology) by top world universities in their spare time for free. They also provide opportunities to interact with interested students in the same fields to discuss materials and collaborate. Despite these advantages, the issues of student persistence and high dropout rates appear as a key challenge facing MOOCs at this stage. In a recent study in 2014 to assess the dropout rates for courses (including medical courses), Jordan reported an average 6.5% completion rate.<sup>3</sup> However, these low rates were expected for an online education platform where students differ in their educational plans, goals for taking these courses and the importance of certificates to them. In addition, time management also plays an important role in dropout rates in a self-learning environment where most of students are enrolled in regular education

with their usual duties.

The numbers of medical students who participate in such courses and how they perceive them is still unclear. There are only a few studies that report post-medical course demographics. In a recent BMJ paper discussing the role of MOOCs in medicine, Harder showed that most of the current opinions expect an increased role in medical education, especially in premed programs and continuing medical education (CME).<sup>4</sup> At present, there are an uprising number of CME-accredited courses, however there is no academic credit for undergraduates for any MOOCs from any medical school in the US till now. This may be explained by the current debate about the effectiveness of MOOCs with its lecture-based learning style to cover all aspects of medical education, including the clinical part which necessitates patient interaction.

Flipped classroom, which is a newly introduced learning model that allows students to watch the lectures online at their home and leave class time for concept discussion with the instructor, has been proposed to be a more suitable model for medical education.<sup>5</sup> This new model permits more interaction between students and instructors (which is weak in MOOCs) promoting active engagement and shifting learning style from passive to interactive. This may save students' short learning time and involve them in more activities that will enrich their clinical skills. However, MOOCs still have the advantage of reaching a massive number of students which is deficient in flipping classroom model with its need to on-campus education along with its limited student registration.

In developing countries, a lot of expectations have been made on the role MOOCs may play in overcoming the lack of access to high quality education in these countries with their massive offer of free courses. Dr. Carol Aschenbrener, one of the medical MOOC instructors, hopes that MOOCs will be considered a good choice that will "help draw more low-income students to medicine and perhaps ease the shortage of doctors."<sup>4</sup> However, the fact that MOOCs present only theoretical background about the topic discussed with low ability to deliver clinical training raises questions about this expected role. The currently available demographic data show low participation from developing countries. Coursera's report showed that most of the participants were from developed countries, especially the United States and Europe, with low participation from Asia and Africa. This was attributed by Liyanagunawardena et al., to be due to complicated sets of conditions, such as lack of access to digital technologies, language, culture, computer literacy and infrastructure, among others.<sup>6</sup> More efforts are needed to address these problems and ensure that MOOCs reach in an efficient way to these countries.

In conclusion, MOOCs represent a great opportunity to spread high quality education to all students everywhere. Although it is still new, great steps have been achieved in its establishment. In medicine, there is an uprising role of these courses in medical education especially CME. However, it is important to address more specialized medical courses with curriculum-based style and to offer credits either for undergraduates or postgraduates to attract more students and solve the issue of dropouts. In addition, although MOOCs will not be sufficient to

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*Submission: Jul 8, 2014  
Acceptance: Aug 4, 2014*

solve the lack of medical workers in developing countries, they still represent a hopeful opportunity that we can build upon.

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**Acknowledgments:** None.

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

**Author Contributions:** Conception and design the work/idea, Analysis and interpretation of data, Write the manuscript and Approval of the final version: OA.

**Cite as:** Aboshady O. Massive Open Online Courses and Medical Education. *Int J Med Students*. 2014 Jul-Oct;2(3):142-3.

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## The Clinical Eye: A Need to Improve the Teaching of Semiology in Undergraduate Medical Education

To the Editor,

Undergraduate medical education is essential for the proper development of professional competencies and skills among medical students. The complexity of today's challenges requires that medical professionals be equipped with the knowledge and skills to address the contingency of diseases, epidemics and disasters currently affecting global public health. Excellent undergraduate medical education and training is necessary to enable the development of future health professionals who are able to provide exceptional medical care.<sup>1</sup>

Medicine is a combination of science and art. The main objective of a physician is to cure patients, or at least alleviate their symptoms and discomforts, giving them a better quality of life. The first step of the overall medical approach is to make a diagnosis based on clinical signs and symptoms. A correct diagnosis allows for the institution of an appropriate therapeutic approach and a better prognostic evaluation of the diagnosed condition. Thus, it is of grave importance that physicians are well trained in order to avoid incorrect diagnoses which can lead to behaviors or decisions that can potentially endanger a patient's health.<sup>2,3</sup>

Semiology is the art of diagnosis that allows for the development of well-defined skills required for the successful application of the clinical method: communication, detection, interpretation, diagnosis and intervention. It is the branch of medicine devoted to the study of the various pathological manifestations (symptoms and signs), finding them (semiotechnique), grouping them into syndromes and giving the subsequent interpretation (clinical propaedeutics), all of which are crucial to make or guide the disease diagnosis.<sup>1,2</sup> A relevant concept of "clinical eye" is defined as the semiological competence which consists in the use of the senses to make the diagnosis of diseases. While there is no standard model of organized steps, there is a general agreement that the process should start with observation.<sup>4</sup>

Currently, the development of increasingly sophisticated medical technologies is leading to an erroneous thought that semiology is not as useful in medical practice as it used to be, dismissing the training in this field of medicine and shifting the focus to more advanced diagnostic tools.<sup>2</sup> Consequently, the high sum of money spent on these diagnostic tools, which include newer and more expensive laboratory and radiological tests, has fueled the dramatic increase in health care expenditure over the last few years, especially in western countries.<sup>5</sup> In addition, preoperative tests are often not utilized in accordance with the clinical criteria. Many of the requested preoperative investigations are unnecessary and have no benefit, resulting in higher costs for the hospital or the patient, congestion in the laboratory department and a high possibility of false positive results.<sup>6,7</sup>

A good semiology can provide accurate diagnosis without additional tests or at least lead to a limited group of differential diagnoses that help in the selection of few very specific tests,

reducing the unnecessary ones and the overall cost.<sup>7</sup> Undergraduate medical education represents the perfect stage to assist and guide the students in the training of their "clinical eye". Regrettably, the teaching of semiology is inadequate in medical schools at present.<sup>1,8</sup> Furthermore, there is heterogeneity in the techniques used for student training, mainly due to the diverse backgrounds of teachers, high teacher turnover and poor teacher training.<sup>8</sup>

Improving the current situation would require an adequate undergraduate medical education and the implementation of new teaching methodologies. For example, it has been shown that systematic observation of figurative paintings improves medical students' observation skills, where students are more likely to provide a complete and accurate diagnosis of clinical photographs of patients with medical conditions that have clearly observable manifestations.<sup>4</sup> Additionally, it is important to promote a greater involvement of students in the process of building knowledge through workshops, conferences, case reports, interdisciplinary forums and problem-based learning.<sup>8</sup> Another strategy is to put more emphasis on practical training to promote students' direct contact with patients and allow for the familiarization with different illnesses and the practice of the skills of anamnesis. We emphasize that any medical semiology training must define well what findings are normal in a healthy patient. To identify what is abnormal, we must first know what is normal.

In summary, it is important to have the mind well-trained so that "the clinical eye" can give us a good diagnosis. Always remember: the best tools of physicians are their own senses.

Carlos Jesús Toro-Huamanchumo,<sup>1,2\*</sup> Laura Rosa Arce-Villalobos.<sup>1,2</sup>

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**Acknowledgments:** None.

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

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

**Cite as:** Toro-Huamanchumo CJ, Arce-Villalobos LR. The Clinical Eye: A Need to Improve the Teaching of Semiology in Undergraduate Medical Education. *Int J Med Students*. 2014 Jul-Oct;2(3):144-5.

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Submission: Sep 17, 2014  
Acceptance: Oct 25, 2014

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## Artist Featured in Volume 2 IJMS: Shelly Mingqian Xie

Whitney Cordoba.<sup>1</sup>

Shelly Xie is the artist of IJMS Volume 2 cover images. She is currently a second-year medical student at the University of Texas Southwestern Medical Center. Shelly earned a Bachelor in Science in Biology with Honors and a minor in Creative Writing from Stanford University where she first created her unique way of impacting medicine by linking art and science.

Her dedication to art began at the age of 12 when she started taking art lessons through which she learned various art media, including acrylic, oil painting, pencil and charcoal drawings. Then in high school, she began a new volunteer service in the hospital where she drew portraits for patients and families of various ages and illnesses. Through drawing over 700 portraits, she brought sparkles of joy to the patients' hospital days while learning from their life experiences they used to share with her. Shelly says she has discovered a greater power of art in helping and healing people. It is also touching hearing Shelly expresses how the experience has led her to choose medicine as a career that would allow her to further contribute to maintaining the health of people.

Since then Shelly wondered how she could better combine her passions in science and art. It was not until she was a senior at Stanford when she joined the Senior Reflection Program that she came up with the creative way of impacting medicine through art. Her project titled "Neglected: A Story of Schistosomiasis Infection in Ghana" is an innovative art modality involving sand animation performance, medicine/global health, and education. Her passion for schistosomiasis - a neglected tropical disease - led her to base the first performance on it. Later, she collaborated with the Pan American Health Organization and created two more sand animations on hookworm and Chagas disease.

The sand animation project has delighted professionals from various fields in national and international meetings of organizations such as TEDx and the American Society of Tropical Medicine and Hygiene, where she received the Communications

Award. The Pan American Health Organization also had her as a special guest to the 52nd Directing Council, where she made two live demonstrations at a plenary session as part of the Art for Research exhibitions, and the list of meetings is growing!

Art and medicine are not mutually exclusive. Art can convey difficult and complex concepts in medicine and health in simpler and more relatable ways for everyone to understand and learn, which indirectly contributes to equity in health and social development. The IJMS is honored to share Initiatives like Shelly's as source of motivation for medical students worldwide. Thank you Shelly for inspiring us throughout this year.



**Scene 1.** "Neglected: A Story of Schistosomiasis Infection in Ghana"  
Cover of IJMS Vol 2 Issue 1.



**Scene 2.** "Neglected: A Story of Schistosomiasis Infection in Ghana"  
Cover of IJMS Vol 2 Issue 2.



**Scene 3.** "Neglected: A Story of Schistosomiasis Infection in Ghana"  
Cover of IJMS Vol 2 Supplement 1.



**Scene 4.** "Neglected: A Story of Schistosomiasis Infection in Ghana"  
Cover of IJMS Vol 2 Issue 3.

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## Acknowledgement of Reviewers of the International Journal of Medical Students, Vol 2, 2014

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The Executive Committee, Editors and Staff of the International Journal of Medical Students wish to sincerely thank the following reviewers for their contributions to the Journal and support to medical students worldwide. Your time and expertise are greatly appreciated.

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