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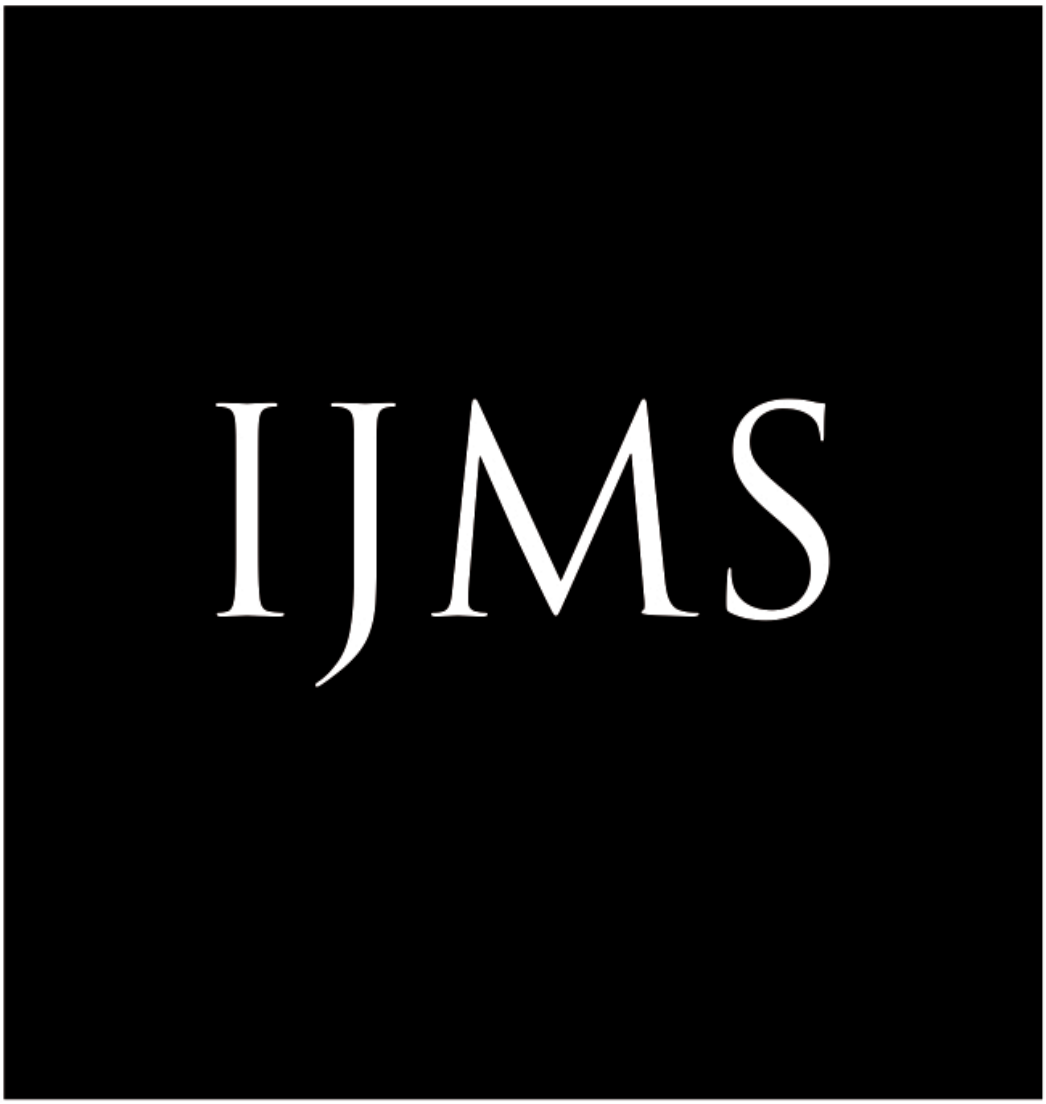

IJMS

International Journal *of* Medical Students

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Original Article

Meloxicam Decreases the Formation of Peritoneal Adhesions in an Experimental Surgical Model in Rats

Luis Alfredo Hernandez Villarroel[1], Henry Fernandez[1], Luisa Cesin[1]

Abstract

Background: Inflammatory adhesions result from an inflammatory response of the peritoneum during an intra-abdominal inflammatory process secondary to thermal or mechanical injury, infection, radiation, ischemia, dissection, abrasion or foreign body reaction. Adhesions produce consequences such as: infertility, intestinal obstruction, and pelvic-abdominal pain. The objective of this study is to evaluate the effects of Meloxicam, a selective cyclooxygenase-2 inhibitor, on the formation of postoperative peritoneal adhesions in an experimental animal model. **Methods:** Twenty female Wistar rats were submitted to laparotomy. Postoperative peritoneal adhesions were induced by scorching the serous surface of the colon. The animals were randomly divided into two experimental groups: one group received Meloxicam intramuscularly for 7 days, and the other served as a control group. They were sacrificed and evaluated at 15 days. **Results:** In the animals given Meloxicam, it was observed that a decrease in number ($p = 0.018$), severity ($p = 0.004$), extension ($p = 0.011$), density ($p = 0.023$), degree of inflammation ($p = 0.002$), vascular proliferation ($p = 0.004$) and fibrosis ($p = 0.029$) of adhesions, compared to the control group. **Conclusion:** In conclusion, this study demonstrated that the administration of Meloxicam intramuscularly significantly decreases the formation of postoperative peritoneal adhesions and, therefore, may be useful in their prevention. The effects of Meloxicam could not only be due to its anti-inflammatory action, but also to its effects on the expression of the Vascular Endothelial Growth Factor.

Keywords: Cyclooxygenase 2 Inhibitors; Experimental Animal Models; General Surgery; Non-Steroidal Anti-Inflammatory Agents; Tissue Adhesions.

About the Author: *Luis Hernández is a doctor of medicine, recently graduated from the University of Oriente. He is winner of the second place in the international competition of research works in the XXVIII International Scientific Congress of the Latin American Federation of Scientific Societies of Medical Students and winner of the first place in clinical cases and the third place in research works in the III Congress of Students of Medicine of the University of the Andes and Regional Course Zone C of the Latin American Federation of Scientific Societies of Medical Students.*

Introduction

Peritoneal adhesions are pathological junctions of connective tissue formed between organs and tissues, and frequently between the omentum, intestines and abdominal wall. The etiology may be congenital or acquired. The acquired adhesions are classified postoperatively or postinflammatory. Inflammatory adhesions result from an inflammatory response of the peritoneum during an intra-abdominal inflammatory process, such as appendicitis and pelvic inflammatory disease. Post-surgical adhesions develop when a tissue is injured by surgical manipulation. [1, 2]

In a prospective study, 93% of patients with a previous laparotomy had peritoneal adhesions, and the incidence of readmissions directly related to adhesions varies from 5% to 20%.[3,4] Each year, 400,000 adhesiolysis procedures are performed in the United States, with a cost in the health system of close to $ 2 trillion in hospitalizations and surgeries. [5]

Adhesions are the result of tissue trauma that may be the consequence of thermal or mechanical injury, infection, radiation, ischemia, dissection, abrasion, or foreign body reaction.6 However, the most important and potential consequences resulting from the formation of peritoneal adhesions are: infertility, intestinal obstruction, and pelvic-abdominal pain. They can affect fertility by distorting the attached anatomy and interfere with the transport of the gamete and embryo. [6]

The most serious of the complications caused by adhesions is small bowel obstruction.[7] Adhesions account for 56% of postoperative intestinal obstructions.8 This surgical emergency has a mortality rate of 3-10% for simple obstruction, and up to 30% when the intestine is necrotic or perforated. In one study, it was evidenced that of 2000 patients submitted to laparotomy 1-2% developed obstruction secondary to peritoneal adhesions in the same year of surgery. The incidence of intestinal obstruction secondary to adhesion formation is 1-10% in 4-6 years after appendectomy, 6% in 5 years after cholecystectomy, 9-25% in 2-10 years following intestinal surgery, and 17-25 % in 5-10 years following proctocolectomy.[8]

However, peritoneal adhesions are not a new problem, surgeons have studied different barrier/pharmacological agents to prevent the formation of adhesions.[9] In this way, different synthetic barrier methods have been used for its prevention.[10,11] Among the pharmacological agents studied are: allopurinol, thymoquinone, phospholipids, spironolacton e, captopril, heparin has been studied.[1, 6, 12-14] Also a variety of steroids and anti-inflammatory agents have been studied, including aspirin, dexamethasone, methylprednisolone, estrogen, progesterone and budesonide.[15] Likewise, the use of hemostatic agents, and the effects of vitamin E and amniotic membrane on the formation of adhesions have been researched.[16, 17] However, none of these pharmacological agents and barrier methods have demonstrated clinically relevant results in reducing chronic pain, decreased infertility, and rate of reoperation.[18]

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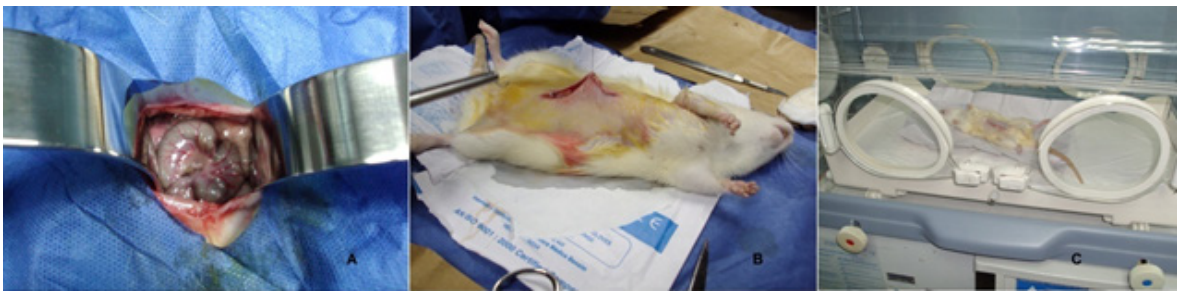
Figure 1. Some of the Procedures Performed During the Adhesion-Forming Surgery and the Immediate Postoperative Period of the Rat. **A.** Exposure of the large intestine of the rat **B.** The skin and subcutaneous cellular tissue were closed with 4-0 nylon. **C.** Postoperative immediately, the experimental animal is in an incubator (medix®, model PC-305) adjusted to 32ćC, enabled for its recovery.



Meloxicam, is a non-steroidal anti-inflammatory categorized as a selective COX-2 inhibitor. It is commonly used in the treatment of acute and chronic pain and inflammation.19 The objective of this study is to evaluate the anti-inflammatory effects of Meloxicam in the formation of postoperative peritoneal adhesions in an experimental animal model. Therefore, in the present study we proposed the use of an experimental model of adhesion formation by serosal abrasion of the colon, having a control group without drug administration and a group to which Meloxicam was given intramuscularly. In light of the above considerations and by its mechanism of action, it is proposed as an alternative hypothesis that Meloxicam inhibits the formation of postoperative peritoneal adhesions; and as a null hypothesis, that Meloxicam does not inhibit the formation of adhesions.

Materials and Methods

An experimental study was carried out in an animal model, in which 20 female rats, Wistar strain, between 250 and 300 g in weight were used. Two experimental rats were kept per cage, with food and water to free demand. The bed of each cage was changed twice a week. They were under cycles of 12 hours light and 12 hours darkness and a temperature in the experimental laboratory of 22ćC ± 2ćC.

All procedures of the research protocol were carried out strictly taking into account the principles for the care and use of laboratory animals, according to the bioethics criteria for the experimentation of the Venezuelan Association for the Science of Laboratory Animals.20

Before the operation, the experimental animals were randomly distributed into two groups consisting of 10 animals each: a control group and a study group.

In each experimental rat, we proceeded to perform a surgical procedure with the goal to induce the adhesion formation process. Each subject was previously anesthetized by administration of 100 mg/kg Ketamine (Keiran®) and 10 mg/kg Xylazine (Rompun®), both intramuscularly.

The abdominal skin was disinfected with Povidone Iodine solution (BETADINE®), prior to the procedure. After, a vertical midline incision measuring 3 cm in length was made, the large intestine of the rat was exposed and the induction of the process of formation of peritoneal adhesions was carried out by a technique already described, which consisted of injuring the serosa of the large intestine by vigorous rubbing with dry gauze (Figure 1A). The rubbing was maintained until the appearance of hemorrhagic points. This procedure was performed in 5 segments corresponding to the cecum, 1 ascending colon segment, 1 transverse colon segment, 1 descending colon segment and sigmoid segment. Each segment was 1 cm in length.

The abdominal wall was closed, suturing the aponeurosis and rectus abdominis muscle with Polyglactin 910 (Vycril®) 4-0; skin and subcutaneous cellular tissue with 4-0 nylon (Figure 1B). At the end of the surgical procedure, each experimental animal was placed in an incubator (Medix®, model PC-305) set at 32ćC, where they lasted for 4 hours with the finality to achieve recovery (Figure 1C).

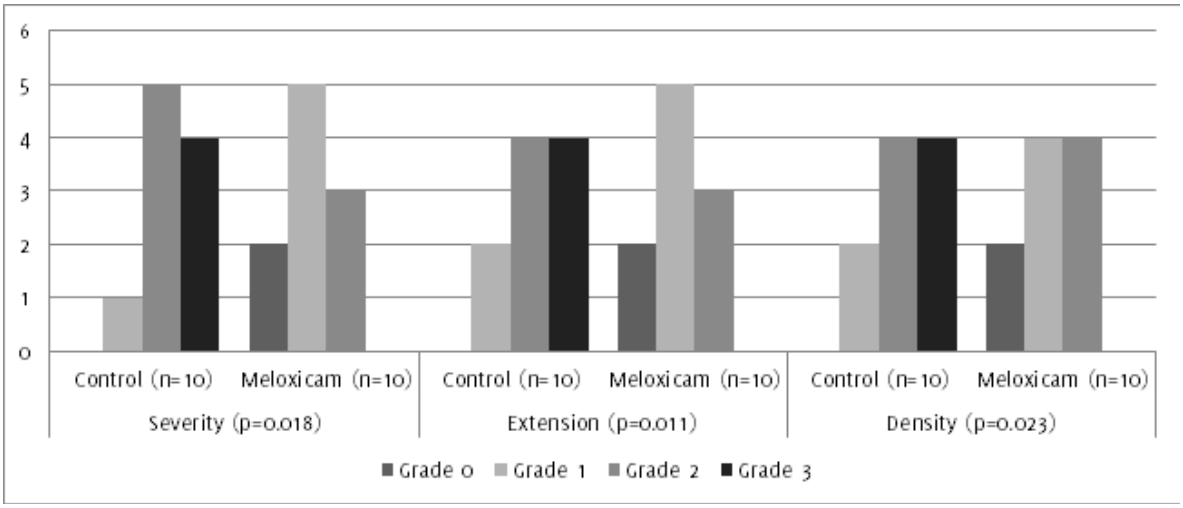
In terms of treatment, the control group had no therapy applied. The study group, was administered Meloxicam (Mobic®, Boehringer Ingelheim) intramuscularly, at a dose of 0.20 mg/kg/day, for 7 days, starting right after the surgery.

All experimental rats were sacrificed at day 15 postoperative, under the effects of anesthesia already described. 1 mL of 7.5% Potassium Chloride was administered via intracardiac injection, via a thoracotomy to achieve exposure of the heart.

An abdominal "U" incision was made by lifting the abdominal wall of the experimental rat with the objective to evaluate the adhesions formed, registering their presence or absence, formation in unmanipulated organs, and whether there were anterior or posterior abdominal wall attachments. Likewise, each of the adhesions presented by the experimental animals of each group was counted.

The degree of severity, dissection and extension were evaluated according to the classification of Diamond.21 According to the severity, it was considered: Grade 0, without adhesions; Grade 1, thin and avascular adhesions were evident; Grade 2, vascularized and dense adhesions were observed; Grade 3, adhesions were firm and cohesive. As for its extension: Grade 0, without adhesions; Grade 1, less than 25%; Grade 2, between 26% and 50%, Grade 3, more than 50% of surface. The density was evaluated by the following: Grade 0, without adhesions; Grade 1, the adhesions were released spontaneously upon se-

Figure 2. Degree of severity, density and extent of peritoneal adhesions. *Statistical significance compared with control group.



paration of the flap; Grade 2, mild to moderate traction was required to separate the adhesions; Grade 3, those that merited adhesiolysis with scissors. Adhesion tissue samples were dehydrated, placed in paraffin, and then 3 micron cuts were made with a rotating microtome (MICROM®). The sections were stained with Haematoxylin and Eosin (H/E) and Masson's Trichrome stain. The surgical pieces were analyzed by a blind observer to the procedure, in the laboratory of Histopathology of the Hospital Complex University Ruíz and Paez, Ciudad Bolívar, Venezuela.

The histological characteristics of the adhesions were determined according to the histological classification of Kanbour-Shakir, which evaluates three aspects: fibrosis, inflammation and vascular proliferation. Firstly, fibrosis is measured by the percentage of occupation of fibroblasts in a dry field of observation (mild ‹33%, moderate › 33% and ‹ 66%, severe › 66%, and no fibroblast proliferation). Secondly, inflammation involves observing the presence of inflammatory cells and classifying it as mild (infiltrating with occasional giant cells, lymphocytes and plasma cells), moderate (giant cells, eosinophils and neutrophils) and severe (abundant inflammatory cells and microabscesses) or absence of an inflammatory component. Lastly, vascular proliferation, defined as the number of blood vessels present per area in 40x magnification or high powered field, classified as mild (blood vessels in less than 33% of the field extension), moderate (in more than 33% and less than 66% of the area) and severe (› 66%) or without blood vessels.22

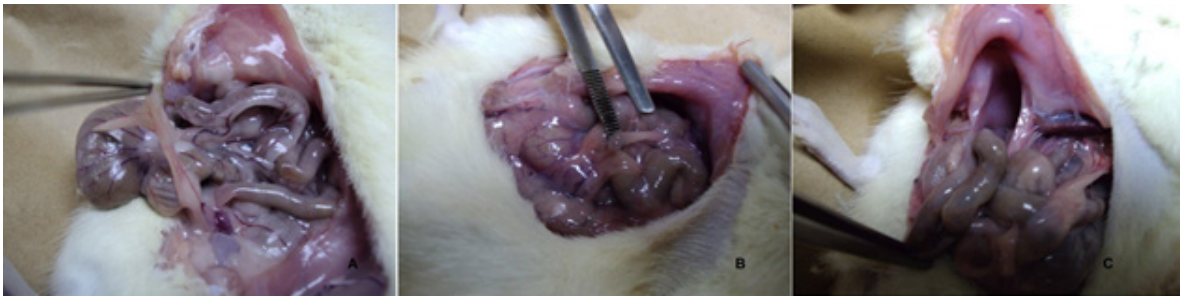
Statistical analysis was performed using the SPSS software (version 23; Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL). The normality of the variables was evaluated by the Shapiro-Wilk test. For the comparison of the means of each group: the quantitative variables with a normal distribution were assessed with the Student's t-test for independent samples; variables not fulfilling a normal distribution were evaluated by the Mann-Whitney U-test; and the qualitative variables were evaluated with the Chi-square test. The confidence interval was set at 95% and the differences were considered statistically significant when the p-value was ,0.05.

Results

All experimental animals completed the study. No congenital adhesions were evident in any of the rats in the first surgical intervention. After the surgical procedure, there were no complications such as wound infections, peritonitis or intestinal obstruction.

Regarding the presence of adhesions formed after the surgical in-

Figure 3. Degrees of Severity of Peritoneal Adhesions Evidenced During Macroscopic Assessment. **A.** Rat of the study group (Meloxicam), which demonstrates a loose adhesion that could be released exclusively with traction. **B.** Strong and cohesive peritoneal adhesions between several thin intestinal loops, with a greater than 50% extension of the abdominal cavity, which required adhesiolysis with scissors for their release. **C.** Adhesions of the small intestine to the anterior abdominal wall (in the control group rat) involving more than 50% of the abdominal cavity with a high degree of severity and impossibility of release, only by adhesiolysis.



duction procedure, 18 of 20 research animals had at least one adhesion. Peritoneal adhesions were formed in all rats (10 of 10 animals) belonging to the control group, while in the rats belonging to the study group (with administration of Meloxicam) the adhesions were evident in 8 of 10 experimental animals.

It was observed that the group of animals that were administered meloxicam after the surgical procedure two animals had only a single adhesion. The total adhesions per experimental group were: 32 in the group treated with meloxicam and 183 in the control group. The mean number of adhesions per group was 18.3 for the control group and 3.2 for the study group (Table 1). These differences were statistically significant (control vs. study group, p = 0.018).

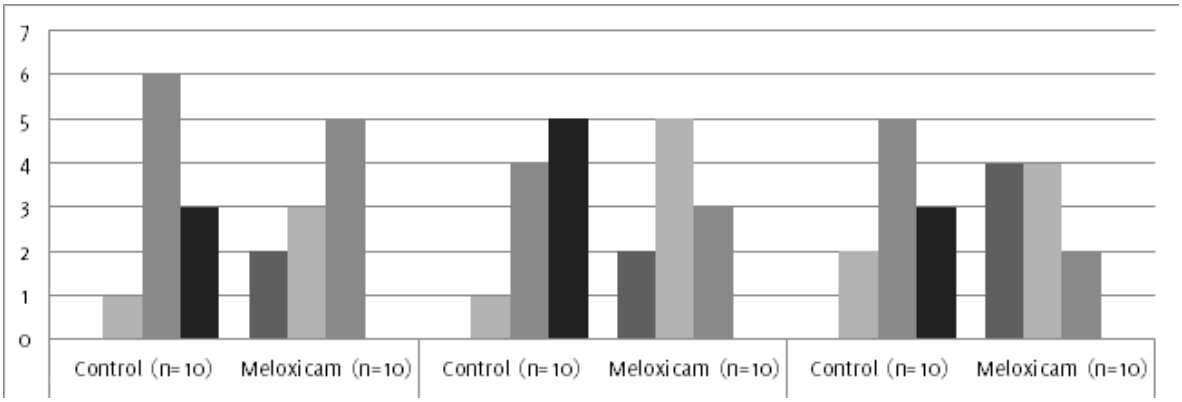
7 of 10 animals in the control group presented with adhesions in unmanipulated organs during the surgical procedure, whereas in the study group none of the experimental animals presented with adhesions in unmanipulated organs. There was a statistically significant difference between the two groups, p = 0.001 (Table 2). The presence of adhesions with anterior or posterior abdominal wall attachment occurred in 4 of 10 animals belonging to the control group. However, this characteristic was not evidenced in the group of animals who were administered meloxicam. There was a statistical difference denoting p = 0.025, in relation to adhesions to the anterior and posterior abdominal wall (Tables 3 & 4).

Regarding the assessment of adhesions, statistically significant differences were evidenced, according to their severity, extension and density (ease for dissection), with corresponding p values: p = 0.004, p = 0.011 and p = 0.023, respectively (Figures 2 & 3).

In the histopathological study (Figures 4 & 5), the development of different degrees of fibrosis was evidenced, depending on the treatment group. Animals treated with Meloxicam had a lower degree of fibrosis, and this difference was statistically significant when compared to the control group (p = 0.029).

Likewise, a statistically significant difference was observed when the inflammation and vascular proliferation were evaluated in both experimental groups, denoting p values of p = 0.002 and p = 0.004, respectively.

Figure 4. Degrees of fibrosis, inflammation and vascular proliferation in postoperative peritoneal adhesions. *Statistical significance compared with control group.



Discussion

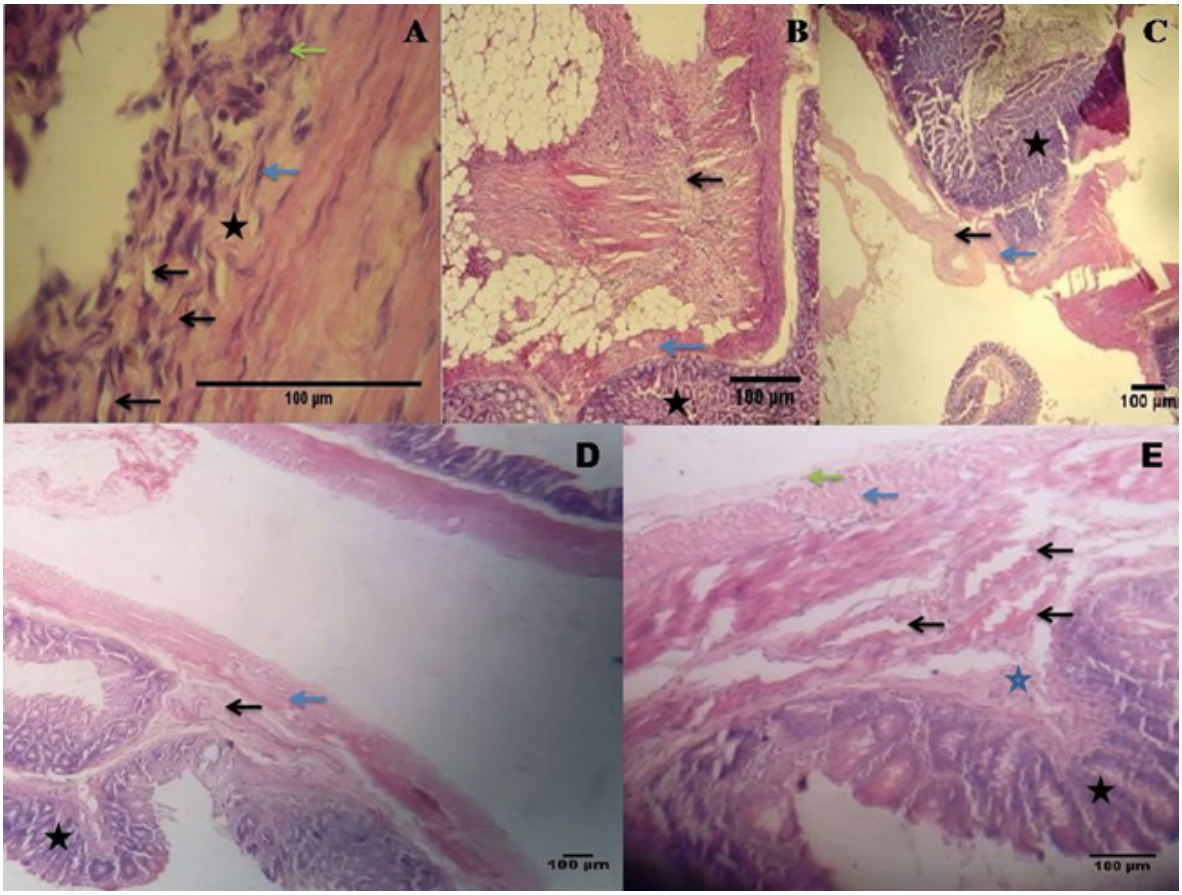
The objective of this study was to evaluate the effects of Meloxicam on the formation of postoperative peritoneal adhesions in an experimental animal model, which consisted of the serous abrasion of the rat colon. The results of the macroscopic evaluation showed that the animals belonging to the group administered Meloxicam developed fewer adhesions and had no adhesions in unmanipulated organs. As for the histological evaluation, it was evidenced that the Meloxicam group under study developed a lower degree of fibrosis, inflammation and vascular proliferation. In contrast, after peritoneal trauma by serosal abrasion of the colon, all rats in the control group developed peritoneal adhesions and greater degrees of severity than the rats given Meloxicam.

The trauma to the peritoneum triggers a cascade of events that begins with the disruption of mast cells, which release vasoactive substances such as histamine that increase vascular permeability.6 In addition, extravasation of a fibrinogen rich fluid occurs from the injured surfaces. Simultaneously, an inflammatory response occurs, with migration of inflammatory cells, release of cytokines and activation of the coagulation cascade. Activation of the coagulation system results in the formation of thrombin, which is necessary for the conversion of fibrinogen to fibrin. Since fibrinolysis is the key determinant in the formation of adhesions. If this does not occur within 5 to 7 days following peritoneal injury, the fibrin matrix persists and is gradually further organized with collagen secreting fibroblasts.[4]

Fibroblasts and myofibroblasts secrete massive amounts of extracellular matrix molecules including fibronectin, hyaluronic acid, glycosaminoglycans, and proteoglycans. This process establishes a bridge between tissues within a few weeks. Further evidence includes vascularization and deposits of collagen in this adhesion bridge formed between the two tissues.[9]

The formation of peritoneal adhesions results from a complex cascade regulated by different cellular and humoral factors. Among the cellular factors are the mesothelial cells, different types of inflammatory cells and fibroblasts. The relationship of these cells and their structural organization is regulated by cytokines, growth factors and signaling molecules. It is widely accepted that in local tissue injury, ischemia, the resulting inflammatory response, and

Figure 5. Images Obtained from the Histopathological Evaluation of Experimental Animals. **A.** Histopathological image representing a sample of tissue with adhesions in which large areas of loose connective tissue and inflammatory infiltrate (star), with presence of giant cells (green arrow), fibroblast (blue arrow) and mild vascular proliferation (black arrow) were observed (Hematoxylin-eosin stain; original magnification X40). **B.** Sample of tissue in which the intestinal mucosa (star), the muscularis externa (blue arrow), areas of fibrosis and presence of infiltration of inflammatory cells (black arrow) were observed (Hematoxylin-eosin stain; original magnification X10) **C.** Sample of tissue in which were evidenced: the intestinal mucosa (star), the muscularis externa (blue arrow) and areas of loose connective tissue (black arrow). (Hematoxylin-eosin stain; original magnification X5). **D.** Histological image belonging to rat, in which no adhesions were observed in the macroscopic evaluation. Highlighted areas include the intestinal mucosa (star), the submucosa (black arrow) and the muscularis externa (blue arrow). (Hematoxylin-eosin stain; original magnification X5). **E.** Histological image in which the intestinal mucosa (black star), the submucosa (blue star) with blood vessels (black arrow), the muscularis externa (blue arrow) and the serosa (green arrow), without inflammatory process, vascular proliferation and fibrosis. (Hematoxylin-eosin stain; original magnification X10).



the promotion of procoagulatory processes such as antifibrinolytic reactions are essential for the formation of peritoneal adhesions.[23]

Peritoneal damage causes an inflammatory response, in which inflammatory cells release cytokines, such as Tumor Necrosis Factor alpha (TNF-alpha), interleukin 1 and 6. These cytokines induce the release of plasminogen activator inhibitor-1 and 2 (PAI-1 and PAI-2) of mesothelial cells, which results in a reduction in Plasminogen activator (Pas) activity. In this way, PAI inhibits fibrinolysis, and fibrin deposits are infiltrated by granulocytes, monocytes and fibroblasts, followed by capillary growth, collagen deposits and adhesion formation.[24]

Likewise, an increase in COX-2 expression has been shown in response to hypoxia in normal peritoneum fibroblasts. However, COX-1 expression remains unchanged in adhesions and fibroblasts under conditions of normoxia and hypoxia. It is hypothesized that hypoxia leads to fibroblasts of the normal peritoneum to acquire a phenotype of adhesions as a manifestation of the marked increase in the expression of COX-2. 25 Hypoxia induces normal peritoneal fibroblasts to produce high levels of PGE-2 and COX-2, an effect that can be prevented by inhibition of COX-2. Therefore, it is considered that COX-2 and its inhibitor may play a role in the postoperative regulation of tissue repair and the development of adhesions.[26, 27]

VEGF is an angiogenic cytokine that participates in the adhesion formation process through the formation of new vessels. It is implicated in early inflammatory responses, tissue repair and remodeling through fibroblast function. It is also important to facilitate fibrin rich matrix deposition, necessary for cell migration and proliferation.[28, 29]

Also, it has been suggested that laparotomy can stimulate the for-

mation of adhesions through a cellular process dependent on mast cells, an inflammatory process that is independent of immediate degranulation. Mast cells are probably not responsible for all locally released VEGF, because this cell produces cytokines that induce the influx of other inflammatory cells that could produce VEGF at the site of the lesion.[28, 29]

It has been shown that dexamethasone, a steroidal anti-inflammatory, in combination with sodium carboxymethylcellulose can prevent the formation of adhesions in a rat adhesion-forming model, inhibiting the migration of inflammatory cells, further decreasing the proliferation of fibroblasts.[30]

Likewise, the use of non-steroidal anti-inflammatory drugs, such as Diclofenac Sodium, has been effective in decreasing adhesion formation in a model of anti-mesenteric border lesion in the rat colon. In this same study, there was a decrease in the development of edema, hyperemia, inflammation and fibrosis.[31]

Similarly, inhibition of COX-2 by the administration of parecoxib, celecoxib, rofecoxib and nimesulide has been shown to decrease adhesion formation in animal models.[32,33,34,35] Guvenal et al. associated the effects of nimesulide in its study to its anti-prostaglandin activity and the reduction of the production of anti-angiogenic cytokines.[34]

However, in a study by Keskin et al., where Meloxicam and Dexketoprofen were evaluated in a rat uterine horn surgical model, it was shown that Meloxicam decreased the development of inflammation. However, despite a decrease in vascular proliferation and collagen formation, there was no significant decrease in adhesion formation.36 In contrast, in the present study Meloxicam was shown to decrease the formation of adhesions, the development of fibrosis, vascular proliferation and inflammation. This may be due to the fact that different techniques and experimental models were used in both studies. In addition, in the same study, Meloxicam was administered 2 days before surgery and 5 days after surgery, whereas in this study meloxicam was given for 7 days after the surgical procedure.
In an experimental model of periodontitis in rats, it was shown that after 14 days of treatment with Meloxicam, there was a decrease in the expression of VEGF expression.37 Similarly, it has been shown that Meloxicam decreases VEGF levels in tumor tissues from animal experimental models.38 In a model of ovarian hyperstimulation syndrome in rats, the results suggest that Meloxicam affects the expression of VEGF in the ovary.39

In addition to the inhibition of the inflammatory process involved in the formation of adhesions in the Meloxicam group, there was also a significant decrease in the development of vascular proliferation. The mechanism is most likely due to a decrease in the production of VEGF by the cells involved in the process of adhesionogenesis, such as mast cells.

Some limitations were evident in our study. The pathophysiological process of peritoneal scarring was one of the limitations, because the mechanisms of adhesion formation in human have not been studied in great detail to warrant a direct comparison to the effects of meloxicam on adhesion formation in rats. The adverse and side effects of Meloxicam was also not examined in the study at the dose (0.20 mg/kg/day) and duration of treatment (7 days) used in the study. Despite the limitations of the study, meloxicam was shown to decrease the formation of postoperative peritoneal adhesions in the experimental model used.

In conclusion, Meloxicam, proved to be effective in the prevention of post-surgical peritoneal adhesions induced in the animal model used. It is a promising finding, based on the pathophysiological knowledge of inflammation, peritoneal healing and the involvement of VEGF in the formation of peritoneal adhesions. Therefore, it is proposed to continue the research of this drug in other models of experimentation, while performing the quantification of inflammatory markers, cytokines in plasma and peritoneal fluid. The final objective of future studies will be to understand the effects, positive or negative, of Meloxicam in the formation of adhesions.

Table 1. Clinical outcomes when comparing the interventions.

Characteristic	Control (n=10)	Meloxicam (n=10)	P-value
Peritoneal adhesions, mean (SD)	18.30 (16.45)	3.20 (2.15)	0.018
Peritoneal adhesions formed in non-manipulated organs*			0.003
Yes, n (%)	7 (100)	0 (0)	0.003
No, n (%)	3 (23.08)	10 (76.92)	0.003
Peritoneal adhesions formed attached to anterior abdominal wall*			0.087
Yes, n (%)	4 (100)	0 (0)	0.087
No, n (%)	6 (37.50)	10 (62.50)	0.087
Peritoneal adhesions formed attached to posterior abdominal wall*			0.087
Yes, n (%)	4 (100)	0 (0)	0.087
No, n (%)	6 (37.50)	10 (62.50)	0.087

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Original Article

Molecular Characterization of Staphylococcus aureus Isolates Obtained from Hemodialyzed Patients at the Hospital de Clínicas of Paraguay: A pilot study

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Abstract

Background: Patients undergoing hemodialysis are susceptible to the nasal carriage of Staphylococcus aureus, increasing the risk of developing infections associated with higher morbidity and mortality. The objective of this study was to describe the frequency of S. aureus carriage in hemodialysis patients and to perform molecular analysis of isolates by applying multiple-locus variable analysis. **Methods:** We conducted a descriptive cross sectional study with non-probabilistic sampling that included 28 hemodialysis patients attending the Nephrology Department of Hospital de Clínicas in Asunción, Paraguay. We obtained clinical data from medical records and interviews with patients. Nasal swabs were collected and analyzed by microbiological and molecular methods. **Results:** The frequency of S. aureus carriage was 50% (14/28), 93% of which (13/14) were methicillin resistant, 57% (6/14) were gentamicin resistant and 36% (5/14) were resistant to more than 4 antibiotic classes. S. aureus carriers showed higher frequency of rhinitis (p=0.02 odds ratio [OR]=6.6 (1.2-34.4)). Seven methicillin-resistant S. aureus isolates had been analyzed by multiple-locus variable analysis, two of them showed identical pattern bands. **Conclusion:** We found a high frequency of methicillin-resistant Staphylococcus aureus colonization and the presence of two isolates with identical profile in the multiple-locus variable analysis indicating the possibility of transmission between patients.

Keywords: Staphylococcus aureus, Hemodialysis, Antibiotic resistance, bacterial typing (Source: MeSH-NLM).

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Introduction

S. aureus is a common pathogen causing bloodstream infections in the hospital environment. The possibility of nasopharyngeal colonization increases the risk of endogenous infections, and is linked to the 80% of cases of invasive S. aureus infections.[1] This microorganism was frequently reported as a pathogen in patients undergoing dialysis and kidney transplantation.[2] These individuals have risk factors for colonization and infection with multidrug-resistant S. aureus because they are exposed to frequent and prolonged use of antimicrobials.[3] Furthermore, the need to use invasive devices such as catheters for venous access are associated with a high risk of bloodstream infections.[4,5] In Paraguay the data about this pathogen in hemodialysis patients is scarce and is limited to local studies that have not been published. Other risk factors for methicillin resistant S. aureus (MRSA) carriage are age . 75 years, prolonged hospitalization, history of repeated administration of antibiotics, type of vascular access, the frequency of hospitalization, immunosuppressive therapy, the use of heparin in the middle of treatment, iron overload, lack of hygiene, comorbidities and proximity to other people carrying S. aureus .[6,7]

Despite the great technological advances, the mortality rates in hemodialyzed (HD) patients remain unsatisfactorily high. Along with cardiovascular disease, infections are the leading causes of morbidity, hospitalization and mortality in this population. The annual mortality rate for sepsis is 100 to 300 times higher in patients with end stage renal disease than in the general population, and there is evidence of the association between nasal carriage of MRSA and poor clinical outcome in HD outpatients.[6-8]

Molecular typing has been used to perform epidemiological studies at the global level. In a specific environment over a short period of time, microorganism typing techniques are used to study nosocomial outbreaks, local transmission, and the relationship between carriage and infection in patients.[9]

The multiple-locus variable number of tandem repeat analysis (MLVA) method can be used for the analysis of genetic variability of S. aureus isolates because it has a high discriminatory power for the characterization of bacterial isolates, and it is based on the variation of 7 different loci. The analysis generates multiple PCR products that differs in size for each allele and produces a pattern of 7 bands like a code bar. Isolates that are genetically distant present differences in their profile of bands and those that are identical share the same pattern of bands.[3,10] The objective of this pilot study was to describe the frequency of S. aureus carriage in hemodialyzed patients attending the nephrology department of the Hospital de Clínicas, and perform the clustering analysis of isolates by the MLVA molecular technique.

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Table 1. Clinical outcomes when comparing the interventions.

	Sensible % (n)	Resistance % (n)
Oxacillin	7%(1)	93%(13)
Erythromycin	21%(3)	79%(11)
Ciprofloxacin	29%(4)	71%(10)
Clindamycin	36%(5)	64%(9)
Gentamicin	43%(6)	57%(8)

Patients and Methods

Study Design

A descriptive cross-sectional pilot study with a non-probabilistic sampling of consecutive cases was performed on October 2013, including 28 patients undergoing hemodialysis in the Nephrology Department of Hospital de Clínicas from Paraguay. The study was approved by the Facultad de Ciencias Médicas Ethics Committee of the Universidad Nacional de Asunción. Patients received information about the study and those who agreed to participate voluntarily signed an informed consent form. For the data collection process, we interviewed patients and revised the medical records. Two patients with missing data concerning this study were excluded. The data collected included the patient's age, sex, years undergoing hemodialysis, white blood cell count, differential count of lymphocytes, neutrophils and eosinophils expressed as number of cells/mm3, day and turn of hemodialysis, use of antibiotics over the last six months, the use of an invasive device, and history of rhinitis.

Collection of samples

We collected the nasal swab of dialysis patients and preserved them in Stuart medium for transportation to the microbiology laboratory. The samples were cultured on blood agar, chocolate agar, mannitol agar and incubated at 37°C for 24 hours. The identification of S. aureus (STAPH-PLUS Pastorex, USA) included the following tests: Gram staining and biochemical test of catalase, DNase, and the agglutination test.

Susceptibility

We have implemented the disk diffusion Kirby-Bauer method according to the Clinical and Laboratory Standards Institute (CLSI) in order to identify the antimicrobial susceptibility. We evaluated the susceptibility to oxacillin, ciprofloxacin, erythromycin, ampicillin-sulbactam, clindamycin, and gentamicin as well. The susceptibility to oxacillin was tested through the use of a cefoxitin disk considered as a breakpoint for resistance if the growing inhibition zone of diameter ,21mm. Susceptibility to vancomycin was not evaluated due to lack of access to methods to determine the minimum inhibitory concentration. Intermediate susceptibility results were considered resistant.

Molecular Methods

We confirmed isolates as S. aureus molecularly through the amplification of a specific 16S rRNA gene, using the protocol and oligonucleotides described by Manfredi et al. 201011. We have extracted DNA from isolated colonies on blood agar by using the commercial kit Wizard Genomic (Promega, USA) following the manufacturer instructions. DNA quantification was performed using the UV spectrophotometer Biowave DNA (Cambridge, UK). The analysis of the genetic variability of S. aureus isolates was carried out by the MLVA technique. This technique involves amplifying seven loci using oligonucleotides and was previously described by Sabat and collaborators.[12] The strain ATCC®29213, negative mecA and producing weak β -lactamase was included as a control in each MLVA assay. We separated the PCR products on 7.5% polyacrylamide gels and performed silver staining following the protocol described by Sambrook et al.[13] We captured digital images with the Kodak Digital Science team CD120 system (Kodak, NYC, United States). We used TreeCon 1.3b software (Ghent University, Gante, Belgium) for the analysis of the band patterns generated and the design of dendrograms.

Statistical issues

We have compared continuous variables such as: patients age, years undergoing hemodialysis, white blood cell count, differential count of lymphocytes, neutrophils, and eosinophils (expressed as number of cells/mm3) between patients with MRSA carriage versus patients without MRSA carriage through the Student's t-test; and dichotomous variables as well such as: patients sex, day and turn of hemodialysis, use of antibiotics over the last six months, the use of an invasive device, and history of rhinitis were analyzed using the chi-square test. Statistical significance was defined as a p value of $p<0.05$ using SPSS 15.0 software (IBM, NYC, United States) for statistical analysis.

Table 2. Resistance profile of Staphylococcus aureus isolates.

	Percentage (n)
More than 1 antibiotic classes	93%(13)
More than 2 antibiotic classes	86%(12)
More than 3 antibiotic classes	50% (7)
More than 4 antibiotic classes	36% (5)

Results

Among the 28 HD patients from the Nephrology Department of Hospital de Clínicas who were part of this study, 50% (14/28) of them were carriers of S. aureus. Antibiotic susceptibility testing identified 92.9% (13/14) of MRSA carriage. Isolates were also resistant to other antibiotics, especially erythromycin and ampicillin-sulbactam, both with 78.6% (11/14). 42.9 % (6/14) of the isolates were sensible to Gentamicin (Table 1). Isolates that showed resistance to more than 4 families of antibiotics were considered multiresistant and included 35.7% (5/14) of MRSA isolates (Table 2).

The analysis of the demographic and clinical data of the hemodialyzed patients classified as: S. aureus carriers and non-carriers showed that only the differences registered in rhinitis OR=6.6 (95% CI: 1.2 – 34.4, p=0.022) were statistically significant (p<0.05) (Table 3).

All the isolates identified as S.aureus by biochemical methods (n=14) were confirmed by the detection of 16S rRNA gene by PCR amplification, with a 100% agreement between phenotypic and genotypic methods. PCR amplification of the 7 loci included in the MLVA method were optimal for cluster analysis in 7 of the 14 MRSA isolates in the study and it gave us the chance to determine the genetic variability (Table 4). The bioinformatic analysis of the band profiles obtained in these isolates generated a dendrogram which is showed in Figure 1. This graphic display has the form of a tree, in which the distance between braches indicates the genetic difference. It can be observed that isolates identified as CR-4 and CR-5 show the same band profile and are clustered together in one branch at the same distance, whereas isolates CR-10 and CR-12, and CR-9 and CR-14 as well, show similar but not identical band profiles and are clustered in groups with branches relatively close to each other (Figure 1).

Table 3. Demographics of Hemodialyzed Patients

	Staphylococcus aureus Carriers (n=14)	Staphylococcus aureus Non Carriers (n=14)
Age (Mean±SD)	41±14	44±18
Dialysis Turn		
Evening	43% (6)	71% (10)
Afternoon	50% (7)	29% (4)
Days of dialysis		
Monday, Wednesday, Friday	43% (6)	71% (10)
Tuesday, Thursday, Saturday	57% (8)	29% (4)
Time of dialysis treatment in years (Mean±SD)	6.1±5.5	5.1±4.6
Use of Arteriovenous fistula	79% (11)	64% (9)
History of different Vascular Access (Mean±SD)	2±2	3±2
Antibiotic treatment in the last 6 months	36%(5)	29% (4)
Rhinitis[a]	64% (9)	21% (3)
Laboratory data (Mean±SD)		
Leucocytes	7510±3767	6012±1531
Neutrophils	5443±3609	3788±1143
Lymphocytes	1509±333	1602±572
Eosinophils	263±302	243±333
Albumin (g/dL)	3.7±0.24	4.01±0.69
Hemoglobin (g/dL)	9.74±1.71	9.08±2.03

[a] Difference was statistically significant.

Discussion

The results showed an alarming frequency of Staphylococcus aureus carriage in hemodialyzed patients (50%), considering that carrying this organism is an important cause of morbidity and mortality in patients who receive hemodialysis. This study portrayed a high prevalence of nasal S. aureus carriage compared with others studies[14,15] that showed between 5-13% of S. aureus carriage.[14,15] However, two studies demonstrated similar carriage rates of S. aureus in hemodialysis patients including Verhoeven et al (58%)[16] and Price et al (49%).[17] The risk of infections in nasal carriers of this microorganism is real and well defined.[18] It is important to point out that the small number of patients included in this study is a limitation and that the results cannot be extrapolated to other hemodialysis services. However, the data regarding this topic is the first published in Paraguay and further research or systematic studies could be done throughout the country in the future.

There are several studies on MRSA carriage, which reported variable data. One meta-analysis by Zacharioudakis et al.19 found 6% of carriage; the frequency in this study was much higher (46.4%). MRSA carriers had an increased risk of mortality in all diseases. This is attributable to the characteristics of the patients that are carriers of MRSA, who exhibit an impaired immune response, and as a consequence lead to an increased

Table 4. Phenotypical and Genotypical Characteristics of Isolates Typed by MLVA.

Patient	Sex	Age	HD Turn	Isolate	O	E	A	L	G	C	MLVA Cluster
4	M	53	Afternoon	CR-4	R	R	R	R	R	R	A
5	M	38	Afternoon	CR-5	R	R	R	R	R	R	A
9	F	57	Evening	CR-9	R	R	R	I	R	I	E
10	M	58	Afternoon	CR-10	I	I	I	R	S	S	B
12	M	37	Afternoon	CR-12	S	S	S	S	S	S	C
14	F	32	Evening	CR-14	R	S	I	S	I	I	F
17	M	20	Evening	CR-17	R	R	R	R	R	R	D

MLVA: Multiple Locus Variable Number of Tandem Repeat Analysis; HD: Hemodialysis; CR: Sample code; M=Male; F=Female; R=Resistant; I=Intermediate; S=Sensitive; O=Methicillin; E=Erythromycin; A=Ampicillin-sulbactam; L=Clindamycin; G=Gentamicin; C=Ciprofloxacin.

risk of infections.[8] Risk factors predispose not only for MRSA carriage, but also for multidrug-resistant gram negative bacilli (GNB) and vancomycin-resistant enterococci (VRE).[20] There is the possibility of vancomycin resistance in MRSA, through the transmission of the vanA gene, as occurred in neighboring countries.[21] In accordance with the high level of MRSA carriage, 32% of the isolates in the study were resistant to all antibiotics used in the Kirby-Bauer test, especially erythromycin (79%). Gentamicin was the antibiotic which had the most effective action in-vitro (43% sensitivity), but the resistance rates were high as well. This study showed similar rates of resistance compared to other countries within the region.[22] The high rates of resistance to antibiotics by MRSA display the capability of the pathogen to carry more resistance genes than MSSA.

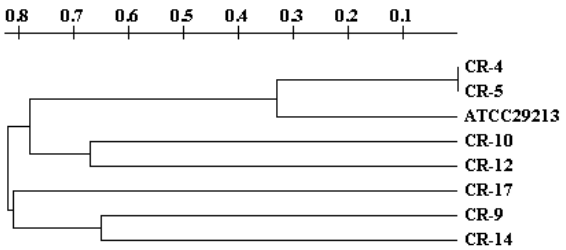
It is important to mention that we did not test the susceptibility to vancomycin in this study; this would be relevant for the epidemiological surveillance and behavior of strains in the hospital environment. In our country, VISA (vancomycin-intermediate S. aureus) or hVISA (heterogeneous vancomycin-intermediate S. aureus) have not been reported yet. This issue could be associated with the restricted access to an automated method to test vancomycin resistance by the minimum inhibitory concentration (MIC) method that is not available in all microbiology laboratories.

By using the MLVA technique, we identified 2 isolates that showed identical band profiles. These isolates also shared the same antimicrobial spectrum (CR-4, CR-5), showing the possibility that they correspond to the same clone. This should be analyzed by the combination of other molecular methods such as field gel electrophoresis (PFGE), multilocus sequencing typing and spa typing.

We discarded the possibility of epidemiological outbreaks due to the low number of isolates having identical MLVA profiles, but we have not excluded any risk of transmission between patients in the service. Internal transmission taking place in the hemodialysis service is a risk, considering that multi-resistant bacteria are circulating. The major goal of MLVA is to determine if isolates are epidemiologically linked and followed over a relatively short period of time to see if they are related or unrelated. In this study, MLVA was helpful for discarding outbreaks in a hospital setting. MLVA is useful, fast, easy to perform, and particularly cheaper to the PFGE method already used in PCR-based assays.[23,24] In respect to other variables that were analyzed in patients, the highest frequency of rhinitis may be related to the fundamental role of eosinophils in the production of itching and predisposition to allergic reactions.[25] Additionally, the nasal carriage of S. aureus produces an immunomodulatory effect that could contribute to airway inflammation and allergic response in patients with allergic rhinitis.[26] In the case of patients undergoing hemodialysis, presenting symptoms or signs may be overlapped by uremic pruritus.[27] Study limitations were the low number of samples included as it was difficult to extrapolate results to all patients undergoing hemodialysis. Nevertheless, as a pilot study this generated the first set of data on the characterization of S. aureus from hemodialysis patients in Paraguay. As a perspective, we are interested in extending the study to other centers throughout the country.

The spread of S. aureus can be controlled through reinforcement of appropriate use of antibiotics, hand washing and laboratory surveillance for S. aureus, particularly in the nosocomial wards, in order to identify sources of outbreaks. The application of MLVA could help us to elucidate if isolates are epidemiologically linked, useful information for confirming or discarding outbreaks in the hospital environment.[28,29]

Figure 1. Genetic Relationship Observed by MLVA among Staphylococcus aureus Isolates



Legend: Dendrogram obtained with the software TreeCon v1.3b. Seven offourteen isolates were processed by the MLVA technique for cluster analysis including a control ATCC®29213). The dendrogram shows the relationship between isolates, the abscissa numbers are indicative of the percentage of genetic variability. For example, between isolates CR-4 and CR-5 there is no variability, but between CR-4 and CR-17 there is 80% genetic variability.

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Original Article

Risk to Develop Type 2 Diabetes Mellitus according to FINDRISC tool in Guatemalan Physicians aged 40-60 years

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Abstract

Background: In Latin America 22.4 million people has abnormal tolerance to insulin, these ones could turn into diabetics if they do not change their lifestyles. Added to this, there are 15 million who present Diabetes Mellitus and this amount will increase to 20 million in 10 years. This epidemic behavior is caused by many factors in which stand out lifestyles, the population aging, and lack of prevention programs. Since 1994, physicians in Guatemala have demonstrated to have inadequate lifestyles in different researches, standing out sedentarism, overweight and obesity, and hypercaloric diets. **Objective:** To evaluate the risk of developing type 2 Diabetes Mellitus using the Finnish Diabetes Risk Score (FINDRISC) in Guatemalan doctors of three medical institutions in the months of June and July 2016. **Methods:** Cross-sectional study, where 176 doctors were interviewed using the FINDRISC. Participant's body mass index and abdominal circumference were measured. **Results:** Mean age was 50 years, 63% (110) male; 55% (96) were sedentary, more than three quarters consumed fruits and vegetables daily, 22% (38) were hypertensive, 10% (17) had a history of impaired glucose and 61% family history of diabetes (108); 47% (82) were overweight and 31% (54) had some degree of obesity. Central obesity was present in 63% (111). There was a statistically significant relationship between age and risk of type 2 diabetes (OR: 3.4 p: 0.001) as well as a relationship between physical activity and abdominal circumference (OR: 2.84, p: 0.001). Out of the total population, 80% (141) of doctors were in some degree of risk, from these, 53% with slightly elevated, 29% moderate, 16% with high and 2% very high risk. **Conclusions:** Eight out of ten doctors studied were at risk of developing type 2 diabetes over a period of ten years. There is a relationship between: age and risk of disease, as well as between physical activity and abdominal circumference.

Keywords: Diabetes mellitus; Physicians; Risk factors (Source MeSH-NLM).

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Introduction

Diabetes mellitus (DM) is a chronic noncommunicable disease, characterized by hyperglycemia, relative deficit (insulin resistance) or absolute deficit of insulin. This chronic pathology requires continued medical care with multifactorial risk reduction strategies beyond glycemic control.[1]

It was estimated globally that in the year 2012 1.5 million people died as a direct consequence of the DM. By 2030, it is projected that this disease will be the seventh cause of mortality and that there will be a worldwide population of 366 million people who will suffer DM. There are about 15 million DM individuals in Latin America; this data will increase to 20 million in 10 years. This epidemic behavior is probably due to several factors including race, change in lifestyles, and population aging. (World Health Organization, WHO. Available from: http://www.who.int/mediacentre/factsheets/fs312/es, updated 2015 Jan; cited 2016 Jul 10).

The Mexican National Health Survey of 2000 shows a prevalence of DM in adults over 19 years of age of 7.5%. It was found that age is directly related to the risk of DM, 2.3% before age 40 and 21.2% after 60 years.2,3 In Guatemala, the CAMDI (The Central American Diabetes Initiative) study found that 24.5% of the participants had a known family history of the disease, the mean Body Mass Index (BMI) was 26.5 kg/m2, the prevalence of DM was 8.4%, and impaired fasting glucose / intolerance glucose was 23.6%. It was demonstrated that, in the population diagnosed with DM, the percentage of obesity and overweight was 78% (47 and 31%, respectively). Also, 55% of the people were sedentary and 27% had insufficient physical activity. These risk factors are the cornerstone to explain the increase of DM in the population.[4]

A research which analyzed these risk factors in physicians in 3 Guatemalan hospitals, evidenced that 53% of physicians were overweight, and 33% Moderate obesity or grade 2, these data were associated with each other, finding that 53% of physicians who were overweight, 14% had average physical activity and 57% had poor physical condition.[5]

According to statistics of Colegio de Médicos Guatemala, during a period of 7 years, the mortality of the medical profession was due in 47% to chronic degenerative diseases among which DM occupied the fourth place; Acute myocardial infarction and cerebrovascular event occupied the Second and third place respectively, these 2 last are common complications of diabetic patients. Of this percentage, 42% of physicians were between the 40 to 60 years of age.[6]

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Table 1. Values of statistical association measures found for related variables in physicians.

Associations*	Odds ratio	CI 95%	p-value
Age – Risk	3.4	1.55 – 7.44	0.001
Gender – Risk	0.84	0.47 – 1.66	0.66
Physical activity – BMI	1.64	0.81 – 3.34	0.17
Physical activity – Abdominal circumference	2.84	1.51 - 5.34	0.001
Diet – BMI	2.78	0.79 – 9.73	0.098
Diet – Abdominal circumference	1.06	0.46 – 2.47	0.88

* Associations: **Age** ‹45 years, .45 years; **Risk** .7 points, **No risk** ‹7 points; **Physical activity** if performed 30 min, does not perform 30 min; **Body mass index increased** . 25 kg / m2, **Body mass index normal** ‹25 kg / m2; **Abdominal circumference normal** (men ‹94cm and women ‹80cm), High (men .94cm, women .80cm); **Diet:** consumption of fruits and vegetables every day, not every day.

There is not any research which has studied the risk to develop Type 2 DM in physicians, even if this specific group has a higher prevalence of the risk factors than other groups. The physicians compromise themselves to take care of the health of the people, but who takes care of them.

This study aims to identify the risk factors for DM and the probability to develop the disease in a period of ten years in Guatemalan physicians aged 40 to 60 years. This study is relevant to increase awareness about self-care of doctors and could potentially increase a better care of patients at risk.

Methodology

A cross-sectional study, carried out in June and July of 2016 in the hospitals: General San Juan de Dios (HGSJDD), General de Enfermedades del Instituto Guatemalteco de Seguridad Social (IGSS zone 9) and Centro Universitario Metropolitano de la Universidad de San Carlos de Guatemala (CUM), where the physicians between 40 and 60 years of age, working in the institutions, were taken as the universe. The three institutions are located in Guatemala City. Two of them are tertiary care level and the third one is an academic institution for medical education. Representing doctors in the Public, Semiprivate and Teaching sectors.

The population estimated was 337 doctors including all the specialties and departments of the three institutions. The sample was calculated by the formula7 n = [Nz2 pq] / [d2 (N-1) + z2 pq], where n = sample to be calculated, N = 337 physicians (population), z = 1.96 (CI of 95%), d = 0.05 (absolute precision), p = 0.5 prevalence of the disease (maximum value, since there are no previous studies), q = 0.5. A statistically representative sample of 180 physicians was obtained, and an adjusted sample was calculated taking a possible 10% rejection with the following formula: na = n * (1/1-R), where na = adjusted sample to be calculated, n = 180 (the sample), R = 10% rejection. An adjusted sample of 200 physicians was calculated, which were distributed proportionally to the population of each institution.

The study excluded physicians who had a definitive diagnosis of prediabetes, type 1 or type 2 DM. The subjects under study were selected by probabilistic, simple random sampling. The Finnish Diabetes Risk Score (FINDRISC) is a tool designed to identify risk factors to develop DM. Data collection was performed using this test. It has been validated in Finland, Spain, Italy and Germany and used in Latin American populations (Venezuela, Cuba and Colombia) to measure the likelihood of developing type 2 DM within 10 years with a sensitivity of 81% and a specificity of 77% 8-14

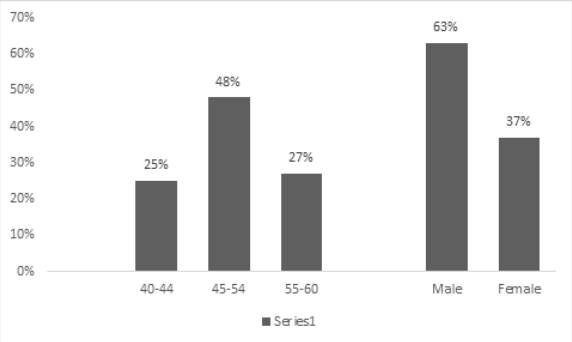
The data collected includes: age, sex, BMI (measured during data collection) and abdominal circumference (measured during data collection), sedentary lifestyle (less than 30 minutes of physical activity daily), diet (daily consumption of fruits and / or vegetables), antihypertensive medication, previous alterations in blood glucose levels, and family history of diabetes. The test assigned a score to each question. The total gives a predictive result for the development of type 2 diabetes in a period of 10 years.

With the statistical software Epi Info® 7.2, the data was analyzed using descriptive statistics. Associations were assessed using 2x2 tables, and they were measured using Chi Square (X2) and the strength of the association with Odd Ratio (OR).

Ethical Considerations

The present study did not perform any intervention in the study subjects. In all cases, the confidentiality of the information collected was maintained.

Figure 1. Distribution of epidemiological risk factors for the development type 2 diabetes mellitus.



Results

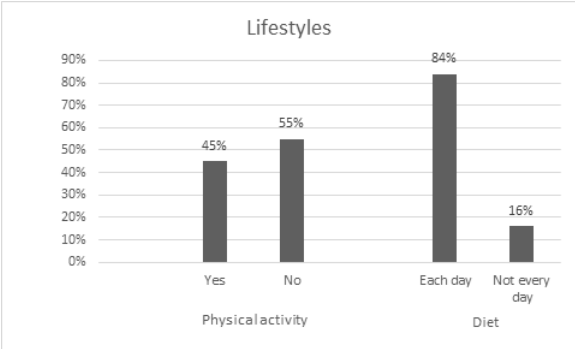
There were interviewed a total of 176 physicians. Among them, 24 (12%) denies their participation in the study. The mean age was 50 years (± 6), 63% (110) were male; 37% (66) female (Figure 1), 55% (96) were sedentary, more than three quarters consumed fruits and vegetables daily (Figure 2), 22% (38) had medication for arterial hypertension, 10% (17) had a history

of impaired glucose, and 61% (108) family history of diabetes, being 42% in first degree of consanguinity and 19% in a second degree (Figure 3); 47% (82) were overweight and 31% (54) had some degree of obesity. Central obesity was present in 63% (111), with a mean in males of 96.32cm (±10.5) and in females of 86.14cm (±10) (Figure 4).

There was a statistically significant relationship between age and risk of type 2 diabetes (OR: 3.4, 95% Confidence interval [95%CI] 1.55-7.44) as well as a relationship between physical activity and abdominal circumference (OR: 2.84, 95%CI 1.51-5.34) (Table 1).

Out of the study population, 80% (141) of doctors were in some degree of risk for DM, 43% at a slightly elevated risk (1 in 25 doctors will develop the disease), 23% moderate risk (1 in 6 will suffer from DM), 13% high risk (1 in 3) and 1% high risk (1 in 2 will develop the disease) (Figure 5).

Figure 2. Distribution of the lifestyles in physicians.



Discussion

Diabetes mellitus is a preventable chronic disease where the identification of risk factors is a priority. The present study is the first to be carried out on these risk factors in physicians and it found physicians were sedentary, obese, with an important prevalence of high abdominal circumference, and with a huge percentage of familiar history of diabetes making them susceptible to develop DM2 in 8 out 10 cases.

Within the age range, an average of 50 years was obtained. Only 25% of them were below 45 years old. It is worth mentioning that in the FINDRISC test it gives risk points when the person is over 45 years old, therefore, with the average age of 50 years of the population, is already a population at risk because of age.

More than half of the interviewees did not comply with 30 minutes of daily physical activity; A result similar to the study of the Mexican Social Security Institute, where it was found that 60% of health staff did not perform physical activity.15 In the Villa Nueva study in Guatemala, it was found that 48% (Population without glucose alteration) and 53% (population with impaired glucose) were sedentary; The study Cardiotesis, found a 27.68% of sedentarism in the Guatemalan population.16 This shows that the prevalence of physical inactivity found in physicians is greater than that of the general population of Guatemala and is similar to that found in health staff in other countries of the region.

Regarding fruits and vegetables, more than 3 quarters of the population studied consume them. The daily intake of fruits and vegetables is translated into a diet high in fiber and complex carbohydrates, reducing the risk of suffering DM, the BMI, and waist circumference.17 This was not associated with risk of DM in this study, therefore, in agreement with the literature.

In general, the study population showed a familiar history of diabetes in more than half of the cases. This is an important aspect, since it increases the risk of diabetes and added to other factors (sedentary, overweight, obesity or central obesity), increases the probability of suffering the disease.

Concerning to history of diseases, hypertension has been closely associated with the risk of diabetes mellitus. It was described that 30% to 50% of hypertensive patients were diabetic.18 This means of the 22% of hypertensive physicians found in this research, 11 to 19 subjects will have DM2. The risk increases more and more when there are other associated factors such as central obesity and sedentary lifestyle as mentioned above. However, adequate control of hypertension has been shown to delay the onset of diabetes and its silent micro- and macrovascular complications18,19. For this reason the FINDRISC asks the question "Do you take medication for blood pressure? Emphasizing the control that is carried on the hypertension of the subject. Only with these data could said that approximately 10% of doctors will develop DM2. 9.7% reported a history of altered glycaemia, a higher than expected figure of 7.4% in Latin America20, noting that physicians are more susceptible to insulin resistance than other people, this may be due to large part to genetic predisposition and part to modifiable factors (inadequate lifestyles).

Obesity and overweight statistics reveal almost half of the subjects were overweight and 31% were obese. In comparison, the Peru study conducted in physicians, found a prevalence of overweight 53%, but lower than obesity with 21%. A study done in Mexico on the health staff, found that a percentage of overweight and obesity of 75 %. In Guatemala, evidence published in 1994 showed that 53% of physicians were overweight and 33% obese.5,16,21 This indicates that the data has not changed in other countries and after 22 years in Guatemala, the statistics are still high. From our knowledge, this could be explained in part due to doctors' lack of interest in their health and in changing their lifestyles.

Central obesity, represented by abdominal circumference, an average of 86.13 cm was found for females and 96.33 cm for

Figure 3. Distribution of backgrounds in physicians.

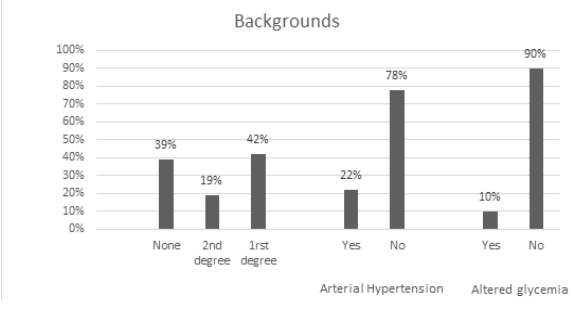
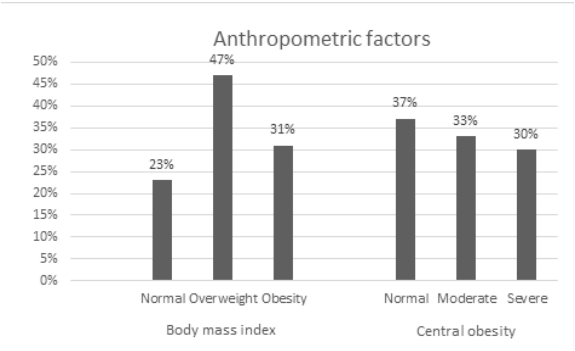


Figure 4. Distribution of the anthropometric factors in physicians.



males. Very similar data can be found when comparing females with populations in Costa Rica and Chile. On the other hand, in the male sex, Costa Rica had an average of 88.1 cm and Chile one of 90.7 cm22-23; this indicates that central obesity is present in female doctors in an equal magnitude to that in other countries, but not the same in the male sex, which shows a higher prevalence.

The prevalence of increased abdominal circumference was 63.1%. The "CADMI" study in Villa Nueva had a 59.9% prevalence and in its hypertensive population. In the study "Cardiotesis" in Guatemala, the prevalence was 53.44% and specifically the urban population of that same study presented 61.13%[16]. This difference between the general population and the urban population is due to different factors, which must be studied and if these are the same in doctors as in the urban population in general. Even so, the number of doctors who presented this factor is worrisome, and is the real reflection of bad diet, lack of exercise, and other unhealthy lifestyles, revealing that long hours of work, having more than one job, increased access to fast food (hypercaloric consumption), among others, as in an urban population, directly influences unhealthy lifestyles and the development of type 2 diabetes, added to the lack of programs for prevention and modification of lifestyles.

The association between age and risk obtained statistically significant values. At an older age, the risk of developing DM increases, taking the cut-off point at 45 years, which is in line with the literature.[1] On average physicians were 50 years old, which makes them susceptible to suffering diabetes.

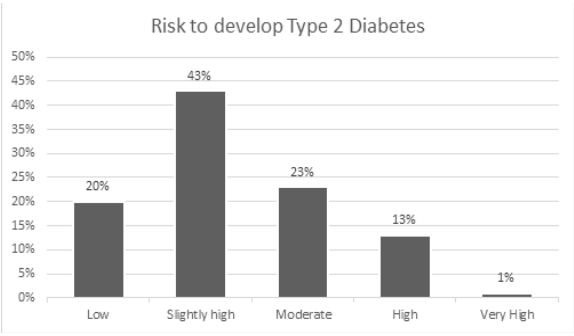
The statistical association between sex and risk of type 2 diabetes was not statistically significant, suggesting that sex does not influence the risk of DM, other studies indicate it only shows a relation when it is associated with overweight, obesity and central obesity.[22]

Physical activity and BMI did not show to be related. This is because of the fact that the test does not evaluate the complete history of the subject, hence it only tests the time the interview was performed (transversal study), reflected that many of the participants were overweight or obese, but many were physically active. Another reason may be that BMI does not differentiate between the percentage of body fat and the percentage of muscle mass and takes it as a single data the weight, that is why there were people who exercised and had a low fat percentage, but a high percentage of muscle mass, and were classified with a BMI greater than 25 kg / m2. In contrast, the association between physical activity and abdominal circumference (central obesity) was statistically significant since this represents only abdominal fat (visceral fat) which is the most specific for the risk of developing DM.

The relationship between diet and BMI, as well as the association between diet and abdominal circumference, did not obtain statistically significant results. The reason is that the variable diet in this study only involves the consumption of daily fruits and vegetables (fiber and complex carbohydrates), which have demonstrated the reduction of risk, decreasing BMI and waist circumference,17 even though from the 84% of the subjects studied that consumed these foods, 63% of them had central obesity and 78% were overweight and obese. This indicates that there are other factors involved in this complex relationship, which according to research would be hypercaloric diets, uncontrolled feeding schedules and high carbohydrate loading at night.[17]

More than 3 quarters of the study population presented risk of developing type 2 diabetes mellitus. The risk was distributed in 43% at a slightly elevated risk (1 in 25 will develop the disease), 23% moderate risk (1 in 6 will suffer from DM) , 13% high risk (1 in 3) and 1% high risk (1 in 2 will develop the disease), which makes them a susceptible population, due in large part to the lifestyles that doctors take throughout their professional preparation, both in undergraduate programs, specialty degrees or subspecialties rand many other factors that increase the risk, together with the lack of intervention by the health system, the entities for which they work and the individual disinterest for health and prevention. Type 2 diabetes mellitus is a disease that can be prevented by knowing the factors present in an individual.

Figure 5. Stratification of the risk of having type 2 diabetes mellitus in 10 years in physicians from 40 to 60 years old.



Within the limitations found by the researchers was a refusal rate to participate in the study of 12%, which exceeds the estimated 10%. Another limitation was that there was no database of doctors where those who had pre-diabetes and diabetes could be ruled out. I addition It could take in consideration other factors like smoking, alcohol consumption, stress level, specialty. Although the measurements could be standardized using the same instruments (digital weighing, measuring rod and metric tape) for all the measurements. Interviewing doctors from three different institutions, makes the study more representative of the medical profession, in addition this is the

first investigation in physicians looking for the risk factors they have to develop type 2 diabetes mellitus.

Conclusions

Doctors are at an average age of 50 years old, present a sedentary lifestyle and most are found to be overweight or obese, adding that more than half present central obesity. Age, physical inactivity and central obesity are risk factors present in physicians to develop type 2 diabetes mellitus. Eight out of ten physicians studied are at risk of developing type 2 DM over a ten-year period, of which 4 are at a slightly elevated risk, 2 are moderate, one are high-risk of DM.

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Author Contributions
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Original Article

Sixth Class Students' Performance and Confidence Levels Before and After Training in Clinical Skills Laboratories

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Abstract

Background: Acquisition of basic clinical skills by undergraduate medical students is becoming of greater concern. Clinical skills laboratories may provide a comfortable environment for training and may allow students to gain adequate performance level. The aim of this study is to evaluate students' performance and confidence levels before and after training of selected procedural skills; also to explore students' expectation towards skills laboratory training. **Methods:** Two questionnaires were conducted before and after training sessions in the clinical skills laboratory, school of medicine, University of Jordan, Amman, Jordan. The skills selected for this study: suture practice, venous access, arterial access, intradermal and intramuscular injection, central venous cannulation, male and female urinary catheterization, nasogastric tube placement and rectal examination. Although fifty-seven 6th year medical students filled the first questionnaire at the beginning before training, only 29 students could attend all training sessions, and fill the second questionnaire. **Results:** For all trained clinical skills, the mean students' performance scores and confidence levels were significantly increased after training (P <0.001). Expectations of students for skills laboratory were high. **Conclusions:** The students' performance and confidence levels were significantly improved after training in the clinical skills laboratory.

Keywords: Clinical skill; Undergraduate medical education; Simulation Training; Medical Students (Source: MeSH-NLM).

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Introduction

The teaching of basic medical knowledge and acquiring the essential clinical skills are important aspects of professional medical practice.[1] After being taught the basic medical knowledge during the pre-clinical phase, the students learn the practical clinical skills by interacting with patients throughout clerkships and clinical rotations during their clinical years. The purpose of the medical curriculum is to allow the students to gain the knowledge, clinical skills and values required for their practicing medical career.[2]

In fact, mastering the basic clinical skills might require adequate opportunities to practice these skills and longer actual clinical, especially inpatient, encounters.[3-4] This is largely limited by time and availability of patients.[5] Furthermore, studies showed that students cannot depend only on clerkships' observations to perform clinical skills competently. [6-8] Therefore, practical training at clinical skills laboratories (CSLs) has gained greater importance in the medical curriculum. [9-10]

In the recent years, CSLs have been established in many medical schools around the world [11-12] as they have become an essential part of the training program.[13] They provide a safe environment and allow forgiveness for the missteps that students may make during procedural skills training prior to real-life practice.[14-15] In addition, CSLs allow students to learn from mistakes as they perform the first clinical skills on manikins. [14] they create a comfortable environment for tutors to demonstrate the clinical procedures step-by-step and to give students the opportunity of performing the skills using manikins[16] as well as repeating them until reaching a good performance level.[17] All of these advantages provide optimal training and preparation for clerkships.[7, 18]

The aim of this study is to determine the effectiveness of CSLs on undergraduate medical students assessing their performance and confidence levels, before and after training of some selected procedural skills. In addition, students' expectation and attitude towards CSLs were investigated.

Methods

Evaluation of a training program designed to increase clinical skills on medical students. In the fall of 2015 (November-December), all (n=57) 6th year medical students, who were in the beginning of their surgical clerkship, were invited to participate in clinical skills training. The study was approved by the Institutional Review Board of Jordan University School of Medicine.

Participants and setting

The medical curriculum at the university is divided into two parts: teaching the basic sciences during the first three pre-clinical years and learning of clinical sciences during clerkships at the last three years. Students directly enroll into clinical rotations after they complete learning the basic sciences.

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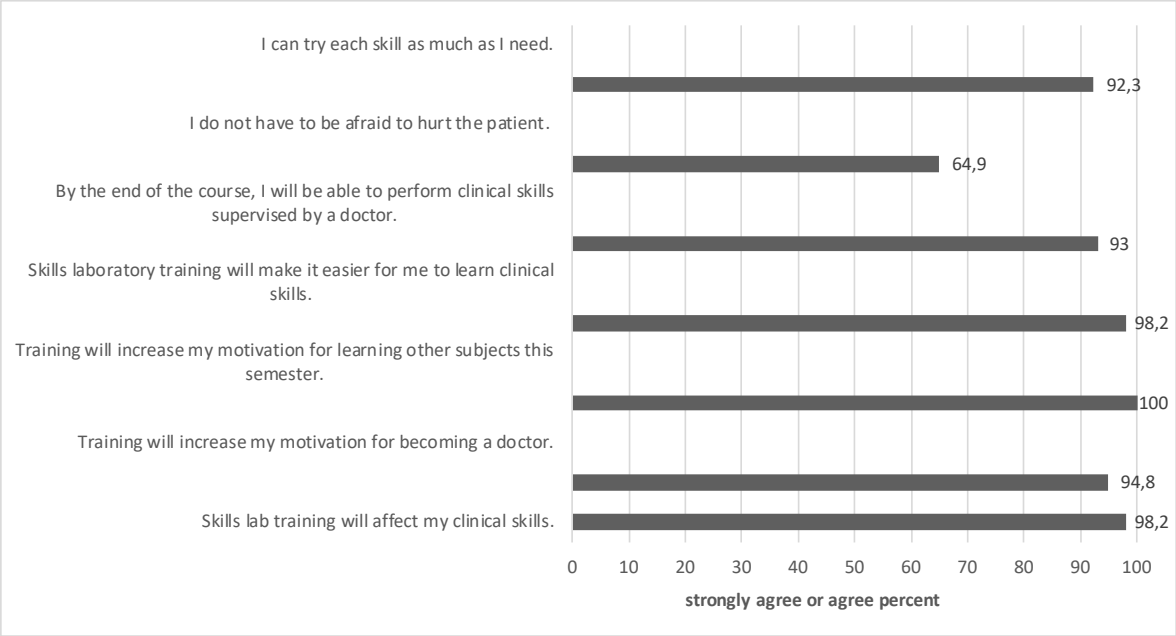
Figure 1. Students' expectations towards skills laboratory before training (n = 57) (My expectations for skills laboratory training are)



All 6th year students who only participated in surgical internship were included for this study. The practical course included eight basic clinical skills, chosen for this study, were taught in three different training sessions, each lasting for two hours. In the first session, suture practice was trained. Venous access, arterial access, intradermal and intramuscular injection and central venous cannulation were trained in the second session. The third session included male and female urinary catheterization, nasogastric tube placement and rectal examination.

The age distribution was homogeneous and sex ratios were similar. Providing training and data collection was carried out by the same coordinator so that the possibility of any bias that could have arisen from different executives was eliminated.

At the beginning of the training, simple clinical background information for each clinical skill was provided by the tutors. After that, the tutors demonstrated the procedures in a step-by-step manner prior to practice. The students then, under the supervision of the tutors, practiced the skills in similar clinical settings using manikins at the CSL. They were allowed to repeat the procedures as many times as they want until performing the skills competently. This is done by the availability of enough manikins and providing sufficient materials for training. The whole training took place at an interactive skills lab affiliated with Jordan University Hospital which utilized trained simulation patients and different models.

Data Collection

This study was planned as a cross-sectional survey. Data was collected using two anonymous questionnaires, which were modified from previously published studies to compare our results with others.19 The first questionnaire was distributed and collected before the beginning of the training sessions and the second questionnaire after the training was completed.

The first questionnaire consisted of general items identifying the students' attitude, expectations regarding skills laboratory training (SLT), and exploring their confidence level with similar items conducted at the second questionnaire. These were investigated as outcome measures. The questionnaire utilized a rating scale ranging from 1 point to 4 points. In addition, students were asked to self-evaluate their skills on a ten point scale in both questionnaires.

Statistical Analysis

Descriptive statistics of the results were computed as frequencies (count and percent), Mean±Standard Deviation and Median depending on the variable studied. Fisher-Freeman-Halton exact test was used for differences between before and after training about distributions of the answers. The differences between before and after training were evaluated using the Mann-Whitney U test with regard to performance score. A P value less than 0.05 was defined as statistically significant. All computations were performed with use of the PASW (ver. 18) program.

Results

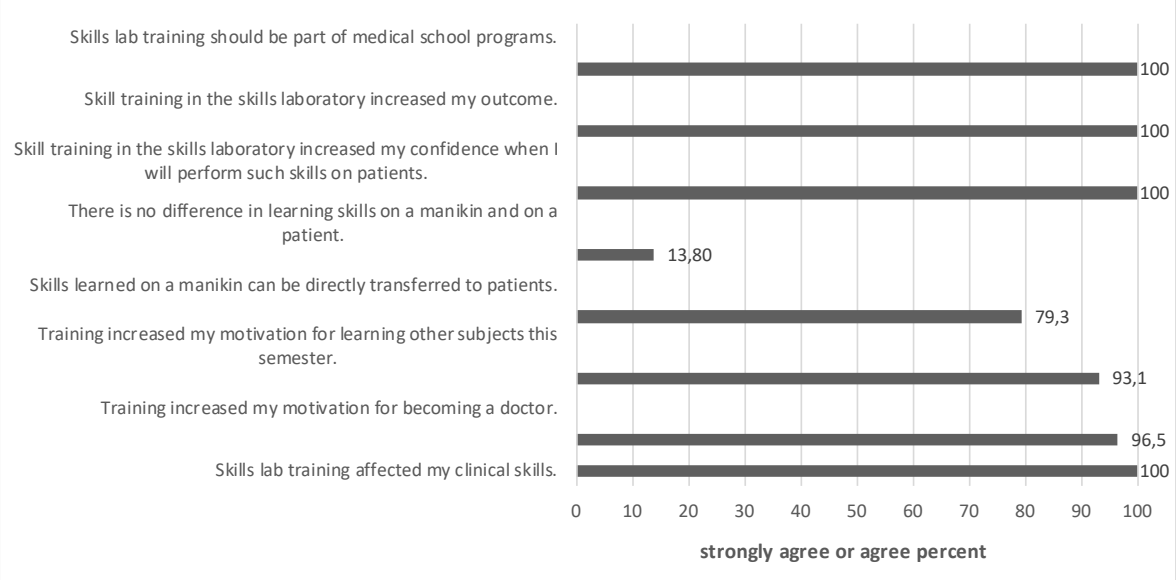
57 volunteer students (27 female, 30 male) answered the baseline questionnaire and 29 students (14 female, 15 male) answered the follow-up questionnaire. Ages of the students were similar to each other (min 23, maximum 25).

Students' expectations and attitude towards skills laboratory before training

All the invited students (n=57) who were in the beginning of their surgical clerkship attended at the beginning and filled the first questionnaire which was distributed before the training sessions. It contained items exploring students' expectations towards SLT. The students answered these items according to a 4-points Likert scale ranging from strongly agreed to strongly disagreed (Figure 1).

Almost all students strongly agreed or agreed that training in skills laboratory would increase their motivation for learning

Figure 2. Students' expectations and attitude towards skills laboratory after training (n=29) (My expectations for skills laboratory training are)



other subjects (100%), would affect their clinical skills and would make it easier to gain them (98%). In addition, most of them believed that training would increase their motivation for becoming a doctor (94%) and expected that they would be able to perform clinical skills by the end of the course (93%).

Students' expectations and attitude towards skills laboratory after training

At the end of the training, 29 students (50.9%) had completed all training sessions and fulfilled the second questionnaire which also contained similar items that determined the students' perception towards skills laboratory after training. The answers were also according to a 4-points Likert scale ranging from strongly agreed to strongly disagreed (Figure 2).

After training, all students also strongly agreed or agreed that SLT affected their clinical skills (100%). In addition; most students informed that training increased their motivation for learning other subjects (93%) and for becoming a doctor (96%). These results met what students expected before training. Further, the majority of them believed that skills learnt on manikins could be transferred to patients (79%).

When the students were asked about learning of skills on manikins and on real patients, 13.8% believed that there was no difference, while others disagreed (disagreed or strongly disagreed). This reveals that the majority of students supposed that there was a difference between these two learning environments as the learning on manikins provided a safe and controlled environment to perform skills for the first time. Further, it allowed repeating of the procedures many times. All students stated that training at CSL increased their confidence and outcome (100%). In addition, all of them suggested that SLT should be a part of the medical curriculum (100%).

Confidence level

The students were asked to determine their confidence level about performing the selected procedural skills. Their answers were according to a 4-points Likert scale ranging from Not confident to Able to do independently (Table 1).

Before training the percentage of students who were Not confident was significantly higher ($P < 0.001$) for all selected skills. But after training, for the "Suture practice", "Arterial access" and the "Male and female urinary catheterization" the percentages of students who were somewhat confident, Very confident and Able to do independently were found to be significantly higher ($P < 0.001$). In addition, when we investigated the answers of "venous access", "Nasogastric tube placement" and the "Rectal examination" after training, it was found that the percentage of students who were Very confident and Able to do independently were significantly higher ($P < 0.001$).

After training of "Central venous cannulation", the percentages of students who were somewhat confident and Able to do independently were found to be significantly higher ($P < 0.001$). Furthermore, the percentage of students who were Able to do independently was also significantly higher after the training of "Intradermal and intramuscular injection" ($P < 0.001$). Thus, there is an overall improvement in students' confidence level after training.

Performance level

When we investigated the students' performance level, we asked them to self-evaluate themselves on a 10 points scale before and after training. The mean score for the performance level of each clinical skill was significantly higher after training ($P < 0.001$ for each skill) (Table 2).

Discussion

In this study we investigated the effectiveness of CSLs on the acquisition of basic clinical skills by undergraduate medical students in the course of SLT, and we also explored students' perception towards skills training. Our results showed that

Table 1. Comparison of before and after training responses.

How confident are you with theses clinical skills		Before Training (n=57)		After Training (n=29)		P
		Count	%	Count		
Suture practice	Not confident	43	75.4[a]	1	3.4b	<0.01
	Somewhat confident	12	21.1[a]	19	65.5b	
	Very confident	2	3.5[a]	5	17.2b	
	Able to do independently	0	0.0[a]	4	13.8b	
Venous access	Not confident	9	15.8[a]	0	0.0b	<0.001
	Somewhat confident	37	64.9[a]	7	24.1b	
	Very confident	9	15.8[a]	17	58.6b	
	Able to do independently	2	3.5[a]	5	17.2b	
Central venous cannulation	Not confident	54	94.7[a]	8	27.6b	<0.001
	Somewhat confident	2	3.5[a]	19	65.5b	
	Very confident	1	1.8[a]	0	0.0[a]	
	Able to do independently	0	0.0[a]	2	6.9b	
Arterial access	Not confident	54	94.7[a]	8	27..6b	<0.001
	Somewhat confident	3	5.3[a]	14	48.3b	
	Very confident	0	0.0[a]	5	17.2b	
	Able to do independently	0	0.0[a]	2	6.9b	
Intradernal and intramuscular injection	Not confident	24	42.1[a]	1	3.4b	<0.001
	Somewhat confident	19	33.3[a]	3	10.3b	
	Very confident	13	22.8[a]	10	34.5[a]	
	Able to do independently	1	1.8[a]	15	61.7b	
Male and female catheterization	Not confident	44	78.6[a]	0	0.0b	<0.001
	Somewhat confident	11	19.6[a]	12	41.4b	
	Very confident	1	1.8[a]	14	48.4b	
	Able to do independently	0	0.0[a]	3	10.3b	
Nasogastric tube placement	Not confident	42	73.7[a]	0	0.0b	<0.001
	Somewhat confident	12	21.1[a]	6	20.7[a]	
	Very confident	3	5.3[a]	12	41.4b	
	Able to do independently	0	0.0[a]	11	37.9b	
Rectal examination	Not confident	30	52.6[a]	0	0.0b	<0.001
	Somewhat confident	23	40.4[a]	7	24.1[a]	
	Very confident	2	3.5[a]	6	20.7b	
	Able to do independently	2	3.5[a]	16	66.2b	

** Different letters which are located on the percentages indicate significant differences between before and after.*

SLT has a valuable effect on students' performance level and it increased their outcome confirming previous findings by Remmen et al. [7]

In addition, students perceived skills training highly to increase their motivation for learning and for becoming a doctor. This was congruent with other studies which found that students had good expectations and highly evaluated training in CSLs. [19-20] In the present study, there was a significant increase in students' confidence level in performing clinical skills after practical course supporting previous studies as well. [19, 21-22]

Before the training sessions, our data showed lower overall performance scores by medical students. This is probably due to the limited hands-on experience of basic skills during clerkships, as the students become anxious and fear harming patients when they have to apply first actual performance on real patients.[23] In addition, limited exposure to patients and limited opportunity to practice the clinical skills during clinical rotations may also have a role. Indeed, in medical schools which depend heavily on clerkships' experience to train basic clinical skills, students' performances have been unsatisfactory.[24-25] This indicates that adequate basic skills training cannot be achieved only by clerkship experience. [8]

In a systematic review, Lynagh et al. showed that clinical skills training at the CSL lead to improvements in performance level compared to traditional training. [11] This goes parallel to

our results which showed that students' scores after training were significantly higher and there was an increase in their proficiency as well. This finding suggests that SLT leads to improvement in students' skills compared to the traditional "see one, do one" approach provided by bedside teaching. [13]

In fact, CSLs facilitate skills training and create a safe and controlled environment for medical students to acquire basic clinical skills; they also allow students to receive feedback about their performance and give the opportunity to repeat the procedures until they become competent before progressing to clerkships. Thus, SLT prepares undergraduate students more effectively to perform practical skills in the actual clinical practice and increases patients' safety. [18, 26]

Our results showed that a majority of the students believed that the skills trained in CSL could be transferred to patients. This confirms other findings revealing that basic clinical skills such as intravenous cannulation and nasogastric intubation can be transferred from skills laboratory settings to be applied to real patients. [13, 18] Thus, the gap between preclinical and clinical phase can be overcome.

The fact that a number of students who were in the beginning of their surgical clerkship failed to complete the training sessions constitutes a limitation of our study. Having detected the presence of some students who disagreed or strongly disagreed with many of the questions constitutes another limitation. Additionally, other limitations may include the fact that the differences between different levels of medical school were not evaluated, the lack of randomization, and the diminished number of participants during the follow-ups.

In conclusion, the overall picture of this study reflects the deficiencies of medical students in acquiring adequate competence in performing basic clinical skills during their clerkships. We have shown in the present study that students' performance was significantly improved after training in the CSL. This underlines the need for skills lab implementation in medical schools and to be an integral part of the medical curriculum. Further studies should be undertaken to investigate the maintenance of skills performance after skills laboratory training and transference into real practice.

Table 2. . Descriptive values of performance score tof clinical skills on before and after training.

On a scale of (1-10) performance yourself in the following clinical skills	Before Training				After Training				P
	N	Percentiles			N	Percentiles			
		25th	Median	75th		25th	Median	75th	
Suture practice	57	1	1	2.5	29	5.5	7	8	<0.001
Venous access	57	3	5	6	29	7	8	9	<0.001
Central venous cannulation	57	1	1	1	29	4.5	5	6	<0.001
Arterial access	57	1	1	1	29	3.5	5	6.5	<0.001
Intradermal and intramuscular injection	57	1	3	6.5	29	8	8	9	<0.001
Male and female catheterization	57	1	1	2	29	7	7	8	<0.001
Nasogastric tube placement	57	1	1	2.5	29	7	8	9	<0.001
Rectal examination	57	1	3	5	29	8	9	10	<0.001

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Review

Pathophysiology, Diagnosis and Treatment of Immune Thrombocytopenia

Mihnea-Alexandru Găman,[1] Amelia Maria Găman[1]

Abstract

Immune thrombocytopenia (ITP) is an acquired disorder characterized by isolated thrombocytopenia with a peripheral blood count < 100.000/mm3 in the absence of any obvious initiating or underlying causes, by antibody mediated destruction of platelets and suppression of megakaryocyte and platelet production on the basis of immune deregulation. ITP is idiopathic (primary) in 80% of cases and secondary to several associated disorders in 20% of cases. A diagnosis of exclusion, based on patient history, physical examination, complete blood count and examination of the peripheral blood smear, is used for ITP. The treatment of ITP is indicated in adult patients with platelet counts below 20.000-30.000/mm3, with bleedings or risk for bleeding. First line therapy is represented by corticosteroids, intravenous immunoglobulins and intravenous anti-RhD. Second-line treatment is represented by: splenectomy, inhibition of the monocytic phagocytic system therapy, immunosupressive therapy, anabolic steroids, anti-CD20 therapy, and thrombopoietin receptor agonists.

Keywords: primary immune thrombocytopenia, ITP, guidelines, thrombopoietin receptor agonists, splenectomy, immune thrombocytopenic purpura.

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Introduction

Immune thrombocytopenia (ITP) is an acquired disorder characterized by isolated thrombocytopenia with a peripheral blood count < 100.000/mm3 in the absence of any obvious initiating or underlying causes. 1 Immune thrombocytopenia may be idiopathic (primary) in 80% of cases and secondary to several associated disorders in 20% of cases: chronic or acute infections, vaccination, autoimmune disorders, immunodeficiency diseases, lymphoproliferative diseases, drugs. The Immune Thrombocytopenia International Working Group consensus divided the disease into three phases: newly diagnosed ITP (less than 3 months from diagnosis), persistent ITP (between 3 months - one year from diagnosis) and chronic ITP (more than one year from diagnosis). 2 The purpose of this manuscript is to review the literature regarding the pathophysiology, diagnosis and treatment of immune thrombocytopenia and to provide essential guidelines for students in medicine and young physicians, taking into consideration that few data is available on the management of patients suffering from ITP.

Search Strategy and Selection Criteria

A literature search was computed by two independent investigators using the MEDLINE database, PubMed, and Google Scholar search services with the following key words and word combinations: immune thrombocytopenia, immune thrombocytopenic purpura, ITP, ITP treatment, ITP guidelines, ITP pathophysiology. Inclusion criteria incorporated relevant articles in English, published in between 1st January 2004 and 1st August 2016, that addressed ITP as their main theme (pathophysiology, diagnosis and treatment). The educational program as well as congress abstracts of the European Hematology Association and ITP working group were also consulted for inclusion in this manuscript. The exclusion criteria were case reports, unavailability of any full article, unclear presentation, non-relevant studies and reports of different languages other than English. The common features were assembled into this present review.

Pathophysiology

Although the pathophysiology of the primary ITP is still unclear, the disease is characterized by an antibody mediated destruction of platelets and a suppression of megakaryocyte and platelet production on the basis of immune deregulation. [3, 4] Both genetic and environmental factors are involved in the production of autoantibodies. A predisposition to autoimmunity, induced by genetic factors, exists and is associated with environmental factors (infection, inflammation, mimicry) which trigger an immune response represented by activated B cells, shifted Th1/Th2 balance, and increased phagocytic activity. Platelet-specific autoantibodies are directed against GPIIb/IIIa (which contains important B-cell and T-cell determinants and seven immunodominant epitopes), GP Ib/IX or other platelet glycoproteins. [4] Antiplatelet antibodies mediate the accelerated clearance from the circulation through the mononuclear phagocytic system. Cellular immunity is disturbed, T-cell and cytokine profiles are shifted towards a Th1/Th2, Tc1/Tc2 and Th17 pro-inflammatory immune response and a reduction in suppressor T-regulatory cells is involved. [3]

The pathophysiology of secondary immune thrombocytopenia, more complex than the one of the primary immune thrombocytopenia, is cause dependent. In chronic infection with Heli-

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cobacter pylori, immune thrombocytopenia is the result of antiplatelet autoantibodies produced by molecular mimicry to H. pylori antigens such as CagA, which induce platelet aggregation and platelet expresion of p-selectin and phosphatidylserine by some strains of H. pylori, associated with susceptibility to the infection of the human host (variation in Lewis antigens at the host mucosal surface, variation in the patient's individual HLA) and an increased phagocytic activity of monocytes and decreased FcγRIIb. Hepatitis C virus (HCV) and human immune deficiency virus (HIV) can provoke anti-HCV and anti-HIV autoantibodies respectively that cross-react with platelet glycoproteins and form immune complexes. [3] Acute infections (Epstein Barr virus, varicella zoster virus, influenza virus) or vaccination induce immune thrombocytopenia by molecular mimicry and/or immune stimulation by specific antigen exposures that tip the immune response to break tolerance to platelets in susceptible persons. [3]

Autoimmune disorders, such as systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome and rheumatoid arthritis are associated with immune thrombocytopenia are characterized by immune deregulation such as the shift in Th1/Th2 balance, increased Th17, and altered T-cells regulatory profiles. Immune thrombocytopenia from SLE is determined by the anti-GPIIb/IIa antibody-mediated platelet destruction and by the inhibition of megakaryopoiesis by antibodies directed against the thrombopoietin receptor (CD110, cluster of differentiation 110). [5] Primary ITP is also a hematological feature of an auto-immune condition entitled antiphospholid syndrome, in which patients are at risk of developing arterial or venous thrombosis, as seen in a systematic review and meta-analysis conducted by Moulis et al. An association (strong if lupus anticoagulant was present, and weaker, but still present, if anticardiolipin antibodies were found) between the presence of antiphospholipid antibodies and the occurrence of arterial or venous thrombosis. [6]

Some authors also believe that oxidative stress can be involved in the development of ITP, since reactive oxygen species that are excessively produced attack fundamental components of the cell such as proteins, which are highly immunogenic and may induce autoantibody production. [7, 8] In small group of 24 patients, external administration of antioxidants via antioxidant supplements and a healthy diet improved therapeutic response and patient evolution. [9]

Diagnosis

The first step in the diagnosis of immune thrombocytopenia is performing a blood marrow smear to confirm the low platelet count. If platelet aggregation is shown, a different anticoagulant (EDTA versus citrate) must be used to rule out the possibility of a false thrombocytopenia, a frequent clinical situation in practice. The diagnosis of immune thrombocytopenia is one of exclusion and is based on the patient's history, physical examination, complete blood count and examination of the peripheral blood smear. 10 The evaluation of ITP requires a basic evaluation and additional tests of potential value. The basic evaluation is represented by: patient, family and medication history, physical examination, complete blood count, peripheral blood film, quantitative immunoglobulins, bone marrow examination (in patients › 60 years old, those with systemic symptoms or when splenectomy is considered), blood group (Rh), H. pylori, HCV, and HIV tests. Additional tests which may have a potential value are represented by: antiphospholipid antibodies (Ig G and Ig M anti β2 GPI antibodies, Ig G and Ig M anti-cardiolipin antibodies), circulate lupus anticoagulant, thyroid stimulating hormone (TSH), antithyroid antibodies, antinuclear antibodies, anti-DNA antibodies, pregnancy test in women of childbearing years, polymerase chain reaction for parvovirus and cytomegalovirus (CMV). The determination of thrombopoietin, reticulated platelets, platelet associated immunoglobulin G, bleeding time, serum complement, platelet survival study have unproven benefits. Tests to rule out an important hematological emergency, disseminated intravascular coagulation, must be performed: prothrombin time, Kaolin time, fibrinogen, and platelet count.

The Treatment of Primary Immune Thrombocytopenia

Treatment is indicated in adult patients with platelet counts below 20.000-30.000/mm3, with bleedings or bleeding risk, trauma, surgery, anticoagulant therapy or patients whose profession/lifestyle predisposes to trauma. Therapy is used to increase the platelet count to a safe level (50.000/mm3) and to prevent further bleeding with minimal toxicities. Most immune thrombocytopenic therapies suppress the active B-cells, T-cell and the mononuclear phagocytic system, and are likely to lead to the downregulation of inflammation and tipping of immune balance back towards tolerance. [3] The latest recommendations of the Immune Thrombocytopenia International Working Group consensus for ITP treatment are presented below.

First line therapy is represented by corticosteroids, intravenous immunoglobulins (IVIg) and intravenous (IV) anti-RhD. Corticosteroids (Dexamethasone 40 mg daily for four days every three weeks, or Methylprednisolone 30 mg/kg/day for seven days, or Prednisone 0.5-2 mg/kg/day for two-four weeks) used in combination with IVIg or IV anti-RhD rapidly increase platelet counts in patients with significant thrombocytopenia (‹5.000/mm3) and extensive bleeding. Corticosteroids globally influence the immune system by suppressing T-cell and B-cell reactivity while inducing tolerogenic patterns in T cells, dendritic cells and circulating cytokines. [3, 11] Toxicities vary with the length of administration, having a lower rate of side effects when a short-term bolus therapy is used (23% of patients have a sustained response at 39 months). [2]

Intravenous immunoglobulins or IVIg (0.4g/kg/day for five days or infusions of 1g/kg/day for one-two days) determined in 65-80% of patients an increase of the platelet count within 24-48 hours. [2, 10, 12] The mechanism of IVIg is unclear, but is thought to tip the immune balance back towards tolerance by inducing inhibitory phenotypes in the mononuclear phagocytic system (FcγRIIb) and possibly by inhibiting complement-mediated cell damage, suppressing B and T cells and exerting a direct anti-idiotype effect on circulating functional antiplatelet autoantibodies. [13] Sustained response is typically for three-four weeks, but may persist for months. Common toxicities are represented by hemolytic anemia, headaches, fever, chills, and infusion reactions. Rare toxicities are: aseptic meningitis, acute renal failure, thrombotic events.

Intravenous anti-D (50-75μg/kg) has a similar dose-dependent

response rate to IVIg in four-five days. IV anti-D modulates FcγRs by blocking phagocytic cells via anti-Rh autoantibodies bound to erythrocytes and may modulate immunity by anti-idiotype activity, Fc receptor modulation, cytokine shifts and downregulation of phagocytosis. Therapy significantly reduced the accelerated clearance of platelets with little effect on the platelet production. [14, 15] Common toxicities are represented by mild hemolytic anemia, headaches, fever. Rare toxicities are: intravascular hemolysis, renal failure, disseminated intravascular coagulation, death. The concomitant use of corticosteroids may enhance the platelet response and reduce the side effects. [16]

Second-line treatment is represented by: splenectomy, inhibition of the monocytic phagocytic system therapy (vinca alkaloid regimens), immunosupressive therapy (Azathioprine, Cyclosporin A, Cyclophosphamide), anabolic steroids (Danazol), anti-CD20 therapy (Rituximab), TPO receptor agonists (Eltrombopag, Romiplostim). Splenectomy remains the treatment option with the highest likelihood of producing cure. It is indicated by some authors as first line therapy in immune thrombocytopenia because the procedure appears to be a curative treatment. It is recommended to wait at least six months from diagnosis before performing splenectomy due to the chance of spontaneous remission. Splenectomy removes a large component of the mononuclear phagocytic system, the site of platelet sequestration, and also a lymphoid organ important for immune function, especially B-cell development and restoration of T-cell variation. [3, 17] Splenectomy is associated with a better response in younger patients with no liver sequestration of platelets, 80% of patients responding to treatment in one to 24 days. Response is sustained with no additional therapy in approximately two-thirds over 5-10 years. The patients requiring splenectomy must be vaccinated before splenectomy with antipneumococcal vaccine and after splenectomy should undergo Streptococcus pneumoniae, Haemophilus influenzae type B and Neisseria meningitidis vaccines to prevent sepsis. The complications of the procedure are: hemorrhage, peripancreatic hematoma, subphrenic abscess, wound infection, pneumococcal infection, and thrombosis. Laparoscopic splenectomy reduced complication rates and is associated with faster recovery, but relapse can occur due to an accessory spleen which may require further surgical intervention. [18, 19]

Anti-CD20 therapy (Rituximab) decreases CD20-expressing B-cells and the shift to tolerance, increases regulatory T-cells, diminishes detectable oligoclonality in T-cell population, stimulates CD110 and increases the platelet number. [17] It is used as the standard lymphoma regimen of 375mg/m2 weekly for four weeks. [20, 21] The optimal dose and frequency of rituximab administration for the treatment of immune thrombocytopenia is still unknown. [22] Sixty percent of patients obtained response (40% complete response) in one to eight weeks. Severe side effects include progressive multifocal leukoencephalopathy and reactivation of hepatitis B. Less serious toxicities include first-infusion reactions such as fever, chills and serum sickness. [16]

Cyclosporine A in dose of 2.5-3 mg/kg/day has immunomodulatory effects, a rate of response of 50-80% in small series and moderate and transient side effects. It increases platelet count alone or in combination with prednisone. Azathioprine has an immunomodulatory effect (40% response rate) and needs to be continued for three to six months. Toxicities have a low incidence and are in general mild. Cyclophosphamide induces response in 25-85% of patients in one to sixteen weeks with a sustained response up to 50%. [2]

Danazol and Dapsone are corticosteroid-sparing agents particularly useful in elder patients and at those to which splenectomy is contraindicated.

Vinca alkaloid regimens have highly variable transient response in 10-75% of patients, with a response-time of five to seven days, an average of ten months sustained response and moderate toxicities: neuropathy, neutropenia, fever, thrombophlebitis or inflammation at the infusion site.

Thrombopoietin (TPO) receptor agonists have provided excellent responses in both splenectomized and non-splenectomized patients. [2] They interact directly with the TPO receptor on megakaryocytes to stimulate platelet production and improve regulatory T-cell activity. [23]

Romiplostim is used in a dose of 1-10 μg/kg both in non-splenectomized or splenectomized patients, with a response time of one to four weeks. It is a competitive inhibitor of TPO and binds directly to the TPO binding site on cMPL.

Eltrombopag is used in a dose of 50 mg or 75 mg daily, with a response-time of 14 days. It may induce hepatotoxicity. Dizziness and reversible introversion have also been reported, but it seems that this TPO receptor agonist gives rise to less frequent and less severe side effects than corticosteroid therapy. [24, 25] Side effects of TPO mimetics are represented by the development of bone marrow reticulin fibrosis, venous thromboembolism, myeloid malignancies, rebound thrombocytopenia, and headache.

The preferred approach on the treatment of secondary ITP is treating the underlying disease. Treatment regimens of ITP in patients failing first and second-line therapy are TPO mimetics and therapy with minimal data, considered to have potential or considerable toxicities: campath-1H (fever, chills, rigor, intracranial hemorrhage, cerebral vein thrombosis, infection, severe intravascular hemolysis, death), combination chemotherapy (risk of secondary malignancies, pancytopenia, hemorrhagic cystitis, neuropathy), hematopoietic stem cell transplantation (myelosuppresion, infection, graft-versus host disease, mucocutaneous bleeding, death).

The treatment of ITP in pregnancy - corticosteroids or IVIg are recommended as first line therapy in the first two trimesters when the patient is symptomatic and if the platelet count falls below 20-30.000/mm3. Splenectomy is rarely indicated in pregnancy, but is the best option in the second trimester if absolutely necessary. [2] In neonates with clinical hemorrhage or platelet counts below 20.000/mm3, therapy with a single dose of IVIg 1g/kg induces a rapid response. Rituximab, vinca alkaloids, danazol, TPO-mimetics should be avoided in pregnancy due to teratogenicity.

The emergency therapy requires a high-dose of intravenous corticosteroids and IVIg or, as alternative, platelet transfusion with or without IVIg, vinca alkaloids, emergency splenectomy and anti-fibrinolytics.

Conclusions

The current manuscript reviews the therapeutic guidelines recommended by international experts in patients with immune thrombocytopenia in order to improve treatment outcome as data regarding the management of such patients is relatively scarce. However, there are studies in the medical literature that report several degrees of inappropriateness in how these guidelines are put into practice as, in some cases, recommendations do not always address all the therapeutical obstacles that the clinician encounters when diagnosing and treating patients with ITP. [26]

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The Enduring Value of Research in Medical Education

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Abstract

Evidence-based medicine (EBM) relies on scientific data to guide diagnosis and treatment and is recognized as the current paradigm in medicine. Accordingly, every current and future physician should be knowledgeable about its principles and methodologies. Embracing research and EBM is essential to modern clinical practice; however, trainees and physicians still struggle with the value of research-related courses and knowledge on epidemiology and research methodology is often poor. In this article we provide a cogent discussion of the importance of research as an indispensable discipline in medical education through a detailed analysis of the literature. We review the evolution of medicine towards EBM and discuss the myriad of benefits that research has on medical careers, leadership roles, mentoring relationships, social networking, and personal growth and development. Participation in research contributes to medicine, public health, and society while simultaneously allowing the achievement of a high level of personal satisfaction.

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

Introduction

The publication from the Evidence-Based Medicine Working Group in 1992 defined evidence-based medicine (EBM) as the new paradigm for medical practice.1 Under this paradigm, the decisions regarding diagnosis and treatment are no longer solely dependent on prior clinical experience, but now include an additional factor: evidence. As a result, physicians have needed additional skills to understand and apply published information in their practices and to help produce the continuous flow of research supporting this system. Despite the fact that EBM has been the model of medical practice for the past two decades, knowledge of research methodology and criteria for the critical evaluation of reported evidence often remains poor among students worldwide.2-5 Clinical investigators, who are essential for the final generation of evidence needed to maintain the practice, have been called an "endangered species".6,7 In this article, we discuss many reasons that support the value of research as a foundational discipline in medical education. We also emphasize how physicians-in-training can benefit from this experience and gain skills that can serve as a valuable tool for their future practices. Therefore, we are optimistic that the reader will find this article both informative and inspiring. A practical approach of how to apply this knowledge into practice is listed in Table 1.

Table 1. Framework of topics that will be covered in this review.

Introduction	The relevance of research in the current paradigm of Evidence-Based Medicine.
Medicine: A Paradigm Shift through the Ages	How medicine has evolved to its current paradigm of EBM and the role of research in this setting.
Relevance of Research for Physicians in Training	The importance of research and EBM for medical students at this stage of training.
Implications for Future Career Plans	The importance of research for medical students' future career plans.
Research as a Catalyst for Leadership and Social Networking	Research as an opportunity to interact with leaders in the field and to develop mentoring relationships with individuals.
Elevating Medical Students to the Demand of Current Medicine	How participation in research permits the progression of medicine by helping translate knowledge from bench to bedside.
Concluding Remarks	How to become the future of medicine.

Medicine: A Paradigm Shift through the Ages

Western medicine has evolved parallel to social and scientific advancements as "a varied and changing social and cultural system",[8] which has led the field toward the practice of EBM. After prehistoric humans believed in using magic to heal, Greeks introduced rational explanations for medical phenomena and described illness as a study of its signs and symptoms resulting in the development of "clinical observation",[9] a method still used today. The scientific spirit of the Greeks was rediscovered during the Renaissance and the Enlightenment when medicine evolved from describing generalizations to solving specific questions through experiments, thus advancing knowledge through the scientific method.[9] The knowledge generated by the Europeans was later spread through colonialism during the Industrial Revolution. Advances in Western medicine were then being generated from multiple areas around the world. At the forefront were American scientists and inventors who were propelled by their ideologies of freedom of expression and pursuit of knowledge. Advances in communication that followed the track of the Industrial Revolution led to the construction of a

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unified scientific knowledge worldwide.[9]

In the nineteenth century, after Flexner's analysis of medical education, medicine progressively separated from pure empiricism and became part of modern science with scientific methodology.[10] With the progressive introduction of medical research into clinical practice, "intuition, unsystematic clinical experience, and pathophysiological rationale"[1] were no longer enough, and systematic evidence was required to determine standards of care. As a result, EBM became the new paradigm of medicine.[1] Epidemiology and biostatistics emerged as the fundamental basic sciences supporting clinical research, while the scope of research focused on studying new treatment strategies and optimal care.[11] This shaped the clinical decision-making process and imposed new challenges by requiring every physician to understand the basics of the scientific method and demanding constant research to fuel advances in their field. As a result of the wide recognition of EBM, the Association of American Medical Colleges (AAMC) called for all medical schools to incorporate mandatory education on clinical and translational research in 2006.[11]

History illustrates how the practice of medicine evolved with the development of science and culture. This progress was driven by scientists and natural philosophers (researchers), and this concept remains strong today. By combining descriptive, experimental, and translational methods, research became a significant part of medical practice; thereby illustrating how medicine is an "ever evolving science based on research".[12]

Relevance of Research for Physicians in Training

If the practice of medicine is based on EBM, what does this mean for current and future practitioners? That the language in which medicine is currently written is no longer prose, but scientific in nature. By definition, EBM is "the conscientious, explicit, and judicious use of the most current and best evidence in making decisions about the care of individual patients," and its "practice means integrating individual clinical expertise with the best available external evidence from systematic research".[13] Regulatory organizations usually consider that understanding scientific principles and EBM is necessary throughout medical training.

The Flexner report was pivotal in restructuring medical education in America and describes medicine as a discipline that follows the laws of biology and therefore one that can be studied using the scientific method.[10,14] Flexner highlighted the importance of self-education and learning by doing. By mastering research as a critical tool for developing new knowledge, medical trainees would become critical thinkers who learned to evaluate information for themselves.[10,14] These principles remain current as exemplified by the report from The World Federation for Medical Education (WFME) Task Force on Designing International Standards in Basic Medical Education. This report requires medical schools to "teach the principles of scientific and evidence-based medicine, and analytical and critical thinking throughout the curriculum"[15] and now it is widely accepted that medical graduates should understand the methodology and applications of rigorous research.[16] Evidence-based medicine permeates most categories of competencies required by the Accreditation Council for Graduate Medical Education (ACGME) for completion of a residency program, including patient care, medical education, and practice-based learning and improvement.[17] Acquiring these skills is fundamentally facilitated by involvement in research.

Consequently, the ideal moment to grasp the fundamentals of EBM and research methodology occurs during medical school, and some even advocate for initiation during undergraduate studies.[18] Overwhelmed by curricular requirements, sleep deprivation, and financial concerns, students may perceive initiatives toward understanding research methodology and applying findings to clinical care as an additional stressor to their training. Therefore, students have reported lack of interest towards research, misconceptions of what research entails, or the perception that their time invested will not be reflected by the appropriate recognition.[19-23] Although epidemiology and biostatistics are viewed as relevant knowledge, they lose importance as students progress through medical school, and disagreement on having research as part of their curriculum has been reported.[18,19,24] Furthermore, student involvement in research varies widely among institutions and countries. The proportion of students from a given medical school who participate in research has been reported as 25% in New Zealand, 57% in Canada, and 54.6% with a 35% publication rate in Colombia (personal communication, Program of Medicine and Surgery, Universidad del Valle, September 26, 2013).[21,24] Some schools have adopted specific programs designed to promote research among students with encouraging results. Historical data from Stanford reports a 95% participation in research with a 75% publication rate after research had been encouraged among students.25 Similar research programs during medical school have been implemented at other institutions with positive results.[22,26-36] This information suggests that despite some motivation by students to participate in research, further strategies are needed for medical schools worldwide to promote the participation of students in research, completion of their projects, and divulgation among the medical and scientific communities.

Despite the differences in the proportion of medical students who participate in research, those involved in this activity recognize the numerous skills acquired in the process.[26] Research participation aids in the development of investigational and analytical thinking, critical reading and writing abilities, organization and time management expertise, and communication skills.[31,34,37,38] Research also teaches discipline and responsibility and improves competences required in all aspects of training, such as public speaking and literature searches and evaluation.[37,39] Progressing through the steps in research and publication in a mentored setting facilitates the continuous practice and improvement of the ability to formulate hypotheses, conduct literature searches, understand research techniques, collect data, and critically evaluate the literature. All are practices that teach students to stay current and even advance science and medicine.[22,31,38,40-42] These experiences provide skills incorporated in the student's armamentarium, whether they decide to pursue a career as a community-based clinician or in academic medicine.[27]

Similarly, research broadens a student's perspective towards medicine and its practice while teaching life-long lessons. By

Table 2. Translation to Practice: Suggested applications of the information provided to your medical student life.

Learning about evidence-based medicine allows you to start applying these principles from the beginning of your clinical experience, at the ideal time of your training.
Early participation in research provides a wide variety of skills that will be beneficial throughout your training and professional life.
Understanding research methodology, statistics and analysis allows improvement in data interpretation and application of an evidence-based approach to clinical practice.
The development of research skills fosters greater personal growth and independence.
Participation in research promotes critical thinking, improvement in writing skills, public speaking, self-motivation and problem solving.
The balance of research with school obligations promotes time-management and punctuality.
Research experience will make you a more competitive and successful applicant whether this is for grant applications/obtaining funding as well as residency, fellowship and job applications.
Early involvement equips medical students with research skills needed in residency.
By partnering with faculty in projects you will gain mentors that will support you the rest of your life.
You can learn to have a team approach to medicine by seeing the collaborative efforts between departments.
The review of one's own work teaches the importance of identifying areas of improvement.
Familiarity with research objectives encourages the critical analysis of established practices.
Understanding study design and statistics prepares you for similar topics tested on the United States Medical Licensing Examination (USMLE) exams.
You can participate in local, regional or national research student organizations or journals to strengthen your own skill development as well as start networking.
Cooperation in research efforts prepares for similar roles in professional organizations.
The time spent exploring topics in depth aids in determining if a specialty is of interest to you.

understanding general principles in basic and clinical research, medical students can be more apt to integrate basic and clinical sciences during medical school, a skill that has been shown to contribute to successful learning.[36] Some suggest that "physicians who think scientifically or critically provide the best patient care"[43],and this way of thinking can also achieve a better understanding of the rapid changes in science, technology, and clinical practice.[40] Participation in research also allows exploration of specialties to facilitate evaluation of interest in future training and empowers students to creatively face problems, propose multiple solutions, and assess the implications of published discoveries.[44] These are all essential skills for effective clinical practice. Knowledge of research also facilitates interaction with patients when explaining implications from translational and clinical research to their care and when discussing enrollment in clinical trials.[45] Lastly, these skills also will be applicable to everyday life.[37] Research demands one to think for oneself, an extremely important quality for understanding scientific knowledge, EBM, and clinical practice. Medical students have recognized the benefits of research training for their current and future career, with up to 95% of students rating these experiences positively and reporting significant personal satisfaction.[26,31,40-42,46-48] Thus comprehension and practice of research principles should be a priority during medical school.

Implications for Future Career Plans

Participation in research can impact student career choices by influencing their decision to become a physician-scientist or to practice in an academic center.[31,33,40,41,43,49-52] Eighty-five percent of students who performed a research project as mandatory for graduation reported that the experience impacted their careers.[31] Furthermore, students who are involved in structured training programs, such as the National Institute of Health (NIH)-sponsored Medical Student Research Fellowship programs (MSRFs), or many other school-based or peer-based programs have shown an increased appeal for academic medicine and have greater involvement in further research projects after the experience.[16,18,33,38,50-53] This supports the idea that an early introduction to research fosters future career decisio ns.[16,27-29,33,36,43,46,49,54-56]

In addition to influencing the decision-making process, the experience and publications can help in advancing a medical career and facilitate a successful transition into the highly competitive field of academic medicine.[22] Data from the Program in Clinical Effectiveness (PCE) at Harvard School of Public Health showed that graduates enrolled because research training was needed to advance their careers (66%), and a young age at the time of enrollment (less than 40 years) correlated significantly with receiving NIH grant funding (perceived as an indicator of a successful research career).[57] Requiring research in medical school has shown to significantly increase publication productivity during and after training.[39] In fact, those students who performed research were considered more competitive candidates for future training or job applications.[25,31,32,39,44,58] Furthermore, participation of under-represented minorities in research has been shown to result in a more diverse workforce in academic centers, contributing to the improvement of teaching, patient care, and research. [59]Individuals involved in research at earlier stages can be more successful as clinical investigators or physician scientists. Thus, we believe that implementing effective

strategies to resonate this message to medical students worldwide is essential.

For most medical students, the next step in their careers will be applications to residency, for which experience in research may offer some additional endorsement. There are many factors that comprise a residency application, such as grades and rank for preclinical and clinical courses during medical school, the Medical Student Performance Evaluation (MSPE), United States Medical Licensing Examination (USMLE) Step 1 and Step 2 scores, letters of recommendation, Alpha Omega Alpha (AOA) membership, medical school reputation, awards, research experience, and publications.[60] Interestingly, although research experience was ranked low in the selection criteria when all specialties were considered together, the most competitive specialties ranked research experience highly.[60] Participants with one or more peer-reviewed publications received a significantly greater number of interview invitations than those without one ($p<0.001$).[61] Accordingly, research experience with successful publication is a desirable quality for applicants. Participation in research is valued because of the overall strengths it instills within the applicant. Therefore, admission committees should be viewed as another source of mentorship, emphasizing the role of research in improving medical practice and professional satisfaction.

Research as a Catalyst for Leadership and Social Networking

With participation in research, medical students can interact with some of the most influential people in their fields, learn directly from those leading the waves of knowledge, and set the standards of care. The time spent with these leaders can be a unique opportunity to gain appreciation of science and to learn to question facts. In other words, this time provides an opportunity to learn how to look at the world and how to study it more efficiently. These leaders can also share their passion for research, which is an invaluable experience in and of itself. Mentors can boost the student's career by sharing their knowledge, offering professional advice, and providing support through many other personal interactions. Data suggests that up to 73% of medical students involved in a research project reported developing a relationship that optimized their research experience and went beyond project advising and mentoring, which has been shown to be crucial for pursuing a successful and satisfying academic career.[22,31,41,49,55] This prolonged exposure is mutually beneficial, creating a positive relationship and facilitating better counsel and support for future career plans.

Through interaction with mentors, other principal investigators, scientists, post-graduate students, and peers, medical students can be inspired to do great things themselves, including participation in more research projects, leadership activities in scientific communities, organization of scientific meetings, and involvement in editorial activities, among many others.[62,63] These activities are often channeled by scientific associations empowered by medical students at local, national, and international levels. The first author's personal experience in the Scientific Association of Medical Students of the Universidad del Valle (ACEMVAL), the Colombian Association of Medical Students´ Scientific Societies (ASCEMCOL), the Latin American Federation of Medical Student Scientific Societies (FELSOCEM), the International Federation of Medical Students' Association (IFMSA), and the International Journal of Medical Students (IJMS) has drastically influenced her way of thinking and her career, motivating her to write this article. Such activities serve as catalysts for passionate students who are bursting with ideas and motivation to contribute to society. This opportunity brings together people from different institutions, cities, countries, and continents and harnesses the diverse intellectual power. For example, the International Journal of Medical Students (IJMS), created by an independent group of medical students motivated by experiences in their scientific associations, established the first student-led, peer-reviewed journal to share the scientific production and experiences of medical students worldwide.[63] In addition, these leadership and research experiences uniquely equip students to become the future leaders of medicine and public health, whether as successfully funded investigators, coordinators of multinational clinical trials, or representatives at the forefront of global health projects, catalysts for public health reforms, or other envoys to serve society.

For medical students, excellence comes from doing more in life than just fulfilling the requirements of a curriculum. The intangible and most commonly overlooked experiences are as valuable as those quantified by papers and presentations. A systematic review showed that participation in leadership training programs had positive effects on faculty advancement in academic rank and success in publishing papers.[64] Thus, similar effects have the potential to be realized among medical students participating in early leadership research positions, providing a jumpstart to exercising these roles in their future professional careers.

Elevating Medical Students to the Demand of Current Medicine

Although research is central to the practice of EBM, the AAMC has identified physician-scientists as a "vulnerable population" because of their declining number and higher rates of failure to achieve funding when compared to non-physician investigators.[45] Despite the numerous insights into the molecular biology and pathophysiology of diseases made in the past few decades, much of this knowledge has yet to be applied to clinical practice and public health.[65] Of 101 studies published in six major basic science journals that reported their discovery had novel therapeutic or preventive promise, only five had been licensed for clinical use.[65] The lack of clinical and translational investigators and a less-than-ideal cooperative communication between basic scientists and clinical investigators were reported as significant barriers to the translation of research.[65] Physician-scientists are uniquely qualified to make discoveries by bringing together experimental data from the bench with clinical observations.[43]

To answer these demands, several strategies have been implemented. The AAMC, the NIH, and several non-profit institutions have designed programs to revitalize the physician-scientist pathway.[35,45,66,67] Medical schools offer joint MD-PhD programs or incorporate scholarly research programs to emphasize disciplined research activities in their students.[27,46,54,68] Residency and fellowship programs have established research-oriented tracks to train physician-scientists and achieve both their clinical and

research goals during their training in an attempt to reduce the time to becoming independent investigators.[51,53,69] Therefore, it is important that research, in either a direct or indirect manner, effectively enters into physicians' thoughts to become truly integrated into their lifelong career and is not perceived simply as a fleeting obligation.

In addition, research fulfills a social goal by producing new knowledge to offer better care. This is evident in developed countries where pioneering treatments are conceived and tested. However, there are still many challenges to be addressed at local, national, and international levels, which require solutions from both a clinical and public health perspective. Current global health issues include the rising burden of non-communicable diseases, the effects of climate change, and trade policies. These new burdens are an addition to the unresolved problems of infections, malnutrition, and reproductive health, which continue to evolve in a dynamic and complex global context.[70] Also, the increasing migration of physicians and patients in a world healthcare market makes these challenges more interlinked and interdependent than before, requiring innovative approaches that should include strategies in medical education and healthcare delivery.[71] By promoting more meaningful participation in research initiatives among medical students from all continents, the next generation of physicians, scientists and leaders can continue to develop innovative strategies for management of diseases through international collaboration that address the health problems of people of all nations, both in developed and developing countries. Thus, participation in research promotes a higher perception about the value of personal accomplishment and the rewarding feeling of contributing not only to one's own community but to many others in need.[12]

Concluding Remarks

The majority of first-year medical students may reiterate that their primary reason to enter medicine is to help people and their communities. This concept no longer lies solely in the altruistic doctor who sets off in a romantic adventure to serve society. Instead, the responsibility to address health issues that our communities face and play an active role in their solution lies with all physicians (current and future). While this happens every day in clinical practice, is it enough? As future leaders in medicine, is it not the responsibility of physicians-in-training to do more? It is your turn as a medical student embrace the breakthroughs in medicine and take them to the next level, address the challenges, and "advance in the pathway of creating knowledge to enhance the health of our communities and nations".[72]

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The Use of Activated Charcoal for Acute Poisonings

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Abstract

Poisoning results from the ingestion of or contact with harmful substances including overdose or incorrect use of any drug or medication. Decontamination measures prevent the absorption of the substance from the gastrointestinal tract to minimize systemic effects. Activated charcoal is the intervention most frequently used in the initial management of patients with acute intoxications. The use of activated charcoal has decreased over time, but there may be a subgroup of patients who would benefit from its use. In this review we describe the epidemiology of intoxications, the composition and pharmacology of activated charcoal, indications and dosing for use of single dose and multiple doses of charcoal, contraindications, complications and a summary for recommended use of this measure based on published studies.

Keywords: Charcoal, decontamination, poisoning, toxicology (Source: MeSH-NLM).

Introduction

The National Center for Health Statistics (NCHS) defines a poisoning episode as "the event resulting from ingestion of or contact with harmful substances including overdose or incorrect use of any drug or medication" (Available from: http://www.cdc.gov/nchs/nhis/injury_poisoning/ip_glossary.htm, updated January 25, 2010, cited September 10, 2016). Acute poisonings are caused by ingestion of different toxic substances that are found in products we use at home, industry and the pharmaceutical sector, these substances can be acids, bases, salts, heavy metals, iodine tincture and others numerous chemicals. Poisonings impact the patient's health through either local or systemic effects. Local effects depend on the substance's specific chemical characteristics and structure.[1,2] Systemic effects are obtained when the substance is absorbed and reaches the bloodstream to be subsequently distributed to tissues.[1,2] The systemic effects can be avoided by performing an intervention to prevent the absorption of the substance from the gastrointestinal tract.[1,2] There are several interventions have been designed to prevent the absorption of toxic substances, including gastric lavage or administration of an adsorbent, which are called techniques of gastrointestinal decontamination.[2,3] Of these, activated charcoal (AC) is the most frequently used gastrointestinal decontamination method in the initial management of patients with acute intoxications.[1,2,4] Despite intoxications being among the first causes of accidental death, medical toxicology remains a small subspecialty of emergency medicine and knowledge of these topics among physicians in general can be limited.[5] Here we present a review of the use of activated charcoal for acute poisonings with a practical approach. The MEDLINE, EMBASE and Current Contents/Science Edition databases were searched mainly with the MeSH terms "Charcoal" and free text "Activated Charcoal", "gastrointestinal decontamination" and relevant articles selected based on the title and abstract. Articles were also selected from the references cited in the articles reviewed.

Epidemiology

A recent systematic review of data from the World Health Organization, PubMed and Google reports that unintentional ingestion, inhalation or contact with chemicals caused 346,000 deaths (7,447,000 disability-adjusted life years) from acute poisonings in 2004, of which approximately 71% were estimated to be preventable.[6] National epidemiological sources such as the United States National Center for Health Statistics reported that poisoning was the second leading cause of injury-related death in 2004 and the rate was higher than at any time since 1968.[7] By 2008 poisoning became the first cause of accidental death in the US.5 Data from the US National Vital Statistics System mortality report that deaths from unintentional poisoning increased at a rate of 62.5%, with 95% of these being secondary to drug use, while poisoning by suicide increased by a rate of 10.8%.[8] The American Association of Poison Control Centers' (APCC) National Poison Data System (NPDS) report that in 2014 there were 2,165,142 human exposures reported to the poison control centers, most of which were unintentional (79.4%) and secondary to single-substance exposures. The main intoxication agents in order of frequency were analgesics (11.3%), cosmetics/personal care products (7.7%), household cleaning substances (7.7%), sedatives/hypnotics/antipsychotics (5.9%), and antidepressants (4.4%); which was equivalent to 51.9% being secondary to non-pharmaceuticals and 48.1% to pharmaceuticals. Ingestion was the main route of exposure (83.7%). The rate of single-substance exposure-related fatal cases was 620 for pharmaceuticals compared with 262 for non-pharmaceuticals (70.3% and 29.7% respectively), illustrating how exposures to pharmaceuticals had more severe outcomes. Children younger than 6 years accounted for approximately half of all human exposures (47.7%). Most toxic exposures occurred at a residence (93.5%), followed by the workplace (1.7%), schools (1.3%), health care facilities (0.3%), and restaurants or food

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Table 1. Substances in which Clearance is Increased by Multiple Doses of Activated Charcoal

Amitriptyline
Carbamazepine
Cyclosporine
Dapsone
Dextropropoxyphene
Digitoxin
Digoxin
Disopyramide
Nadolol
Phenobarbital
Phenylbutazone
Phenytoin
Piroxicam
Propoxyfene
Quinine
Sotalol
Theophylline

services (0.2%). Of all the intoxications reported there were 8.01% that had a clinically moderate or major effect or resulted in death. The use of activated charcoal has declined over time and is currently listed as the fourth most common method of decontamination used, after Dilute/irrigate/wash, Food/snack, or Fresh air (46,030 compared to 796,400, 179,470, and 68,722 cases respectively) but it remains to be the first gastrointestinal decontamination intervention employed.[4]

Likewise, the Central Information Security of Chemicals of Colombia reported that in 2011 there were 4442 calls for advice on toxicological emergencies, where 46.4% were secondary to voluntary intoxication followed by accidental poisonings, and occupational exposure corresponded to 7.2% corresponding to 1.76 daily emergencies due to exposure to substances in the workplace, mainly pesticides (CISPROQUIM. Colombian Council of Security: Annual Report on Emergencies 2009. Available from: http://ccs.org.co/interna_cispro.php?idnoticia=142&topcacordeon=8, updated 2016 Jul 7; cited 2016 Jul 7). As illustrated, acute intoxications remain an important cause of morbidity and mortality that vary by location, therefore understanding and applying these concepts in relation to gastrointestinal decontamination can have a large impact on the outcome for these patients.

Composition and Mechanism of Action of Activated Charcoal

Activated Charcoal

Activated charcoal is a mixture of particles which are insoluble and are produced by heating pulverized carbonaceous substances (for example sawdust, peat, or coconut shells) to extreme temperatures (600-900°C). Subsequently this substance is submitted to the "activation phase" by using steam to erode the internal surfaces of the product, this results in an increase of its adsorptive surface area.[1,2] The average surface area for activated charcoal is 800-1,200 m2/g.1 "Superactivated" charcoal may have a surface area of 2,800-3,500 m2/g and can adsorb greater quantities of the substance.[1,9]

Mechanism of Action

Activated charcoal acts like an agent that adsorbs substances localized in the gastrointestinal tract and retains them within the charcoal, thus minimizing the absorption into the bloodstream and reducing or preventing systemic toxicity.[1,2,10,11] The terms adsorption and absorption are therefore used distinctively to describe each process. To ensure contact of the charcoal with the toxic agent prior to absorption by the mucosa it must be administered as soon as possible. Any delay may decrease its effectiveness.[1,2]

The absorptive surface of activated charcoal contains several chemical forms, such as carbonyl and hydroxyl groups, which adsorbs toxic substances with different affinities.[1] Studies in vitro have indicated that several factors can influence its adsorptive capacity, such as temperature, pore size, particle size, surface area, solubility and toxic ionization stage, the pH, the presence of inorganic salts, and the gastric contents; most of which cannot be controlled or modified when providing clinical care to the intoxicated patient.[12]

The effectiveness of activated charcoal depends on multiple factors: the longer time elapsed from ingestion to administration reduces its efficacy, as well as presence of food in the gastrointestinal tract, inherent chemical composition and characteristics of the substance itself (for example lipid solubility) and the presence of other substances that decrease intestinal transit time. In addition, effectiveness can also be altered due to the phenomenon of desorption, which can occur when a complex of activated charcoal and a toxic weak acid change from a highly acidic pH in the stomach to an alkaline pH in the small intestine that leads to release of the substance from the charcoal and thus may lead to some absorption of substance into the body. Some suggest that this phenomenon rarely has clinical significance.[1,12]

Furthermore, volunteer studies demonstrate that the maximum reduction in the absorption of toxic substances was obtained when active charcoal was administered within the first hour of toxic intake.[1,13] Some studies have shown that activated charcoal can be effective up to 4 hours after ingestion but efficacy decreases over time.[13,14] Other studies have shown inconsistent results on the benefit of its administration two hours after the ingestion of the toxic substance.[1,11] Therefore there is a potential benefit of administration of activated charcoal if administered after 1 hour from ingestion. In addition, due to the adsorptive effect and prevention of absorption of toxic substances into the bloodstream, some authors have suggested that AC may enhance the elimination of substances.[12-14] This will be further discussed in section 4.3.

Indications

Use of gastrointestinal decontamination measures in the emergency department continues to be a controversial topic in the toxicology literature.[14] The formal recommendation from the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists in their position paper in 1997 recommended its use only within an

hour of the intoxication and this recommendation was maintained in their subsequent 2005 update.[1,15] There has not been much literature published in this topic over the past 2 decades and therefore under the paradigm of evidence-based medicine there is limited data to support the use of activated charcoal, and some authors have suggested that combined with the low mortality observed in intoxicated patients administration may not be warranted.[14] However, there could be a subgroup of patients who would benefit from activated charcoal and efforts have been made to offer recommendations for patient selection which will be described below.

The two well designed clinical trials evaluating the benefit of activated charcoal had significant limitations. Cooper et al. randomized all patients over 16 who presented within 12 hours of an intoxication to receiving activated charcoal or no decontamination. The study was performed between July 1999 and October 2000 on sequential patients who presented to the Emergency Department at The Canberra Hospital in Australia. Patients were randomized to activated charcoal (AC) or no gastro-intestinal decontamination as indicated by the sealed sequentially numbered envelope contents. The trial recruited 327 patients over 16 months. The most common substances ingested were benzodiazepines, acetaminophen and selective serotonin reuptake inhibitor antidepressants. More than 80% of patients presented within 4 hours following ingestion. There were no differences between AC and no decontamination in terms of length of stay (AC 6.75 h, IQR 4–14 vs. controls 5.5 h, IQR 3–12; p 0.11) or secondary outcomes including vomiting, mortality and intensive care admission.[16] Some of the limitations on this study is that it included patients who were unlikely to develop significant toxicity and would have therefore had good outcomes irrespective of AC and it excluded seven patients with severe toxicity.[14] The second study by Eddleston et al. who conducted a randomized controlled trial comparing outcomes for patients treated with single or multiple doses of activated charcoal (SDAC and MDAC respectively) to no charcoal (no AC). They report no reduction in risk of death from use of multiple dose activated charcoal, with odds ratio of MDAC vs no AC 0.93 (CI 95% 0.69–1.25), SDAC vs no AC 1.05 (CI 95% 0.79–1.40), MDAC vs SDAC 0.89 (CI 95% 0.66–1.19).[17] Unfortunately this study mainly included patients with intoxications from pesticides and oleander so it is difficult to apply these findings to patients who have had intoxications from prescription drugs.[14] No studies have been performed on selected patients based on strict criteria to attempt to identify the subgroup of patients who would benefit from these interventions. A summary of important studies has been performed by other authors and is available for review.[14,18,19]

Single Dose of Activated Charcoal

There are no absolute indications for the administration of activated charcoal.[2] Universal routine administration is not recommended in the poisoned patient.[2,10,11,14,16,17,20] Activated charcoal should be administered in patients who have a history of ingestion of a potentially toxic amount of a substance and present to an emergency department within the first hour of the event.[1,10,11] However, the benefit of its administration on patients out of this time-frame cannot be excluded.[1] The national guideline for acetaminophen overdose in Australia and New Zealand recommend use of AC up to 2 hours after ingestion.[21]

Greene et al,2 suggest that activated charcoal should be administered when all the following criteria are met:

1. Intake of a potentially toxic substance.
2. No contraindications for its use.
3. The ingested substance is susceptible to be adsorbed by activated charcoal.
4. There is high probability that the substance is still in the gastrointestinal tract at the time of administration.
5. The patient is alert and can protect its airway, or has been intubated prior to its administration.
6. The gastrointestinal tract is anatomically and functionally intact.
7. There are no alternative therapies that are safer and/or more effective.

Bailey et al. recommends the implementation of the "Triangle of gastrointestinal decontamination" to determine whether or not to perform gastrointestinal decontamination.22 The triangle can be used to evaluate the risk versus benefit of this therapy and should be applied considering all the variables at the same time and not consecutively.[3,22]

- Will the intake of this substance have significant effects?
- Can gastrointestinal decontamination change the outcome for this patient?
- Can the administration of activated charcoal be deleterious to the patient?

Isbister et al. suggest considering administration of activated charcoal in two groups of patients: One group are cooperative patients where charcoal may reduce length of hospital stay. The other group of patients include those with a life-threatening poisoning that is not easily treated, such as arrhythmias, multiorgan failure, where even a small benefit of SDAC may improve outcomes and they consider it a duty of care to administer charcoal.[14]

Even though activated charcoal has been universally used to adsorb a variety of agents and administration of activated charcoal is considered a low-risk intervention, there are substances which are not adsorbed by AC and therefore it should not be used to treat these intoxications. These substances are: hydrocarbons, acids, alkalis, ethanol and heavy metals.[1-3,12,14] Lapus et al. has used the acronym “PHAILS” to facilitate learning on which intoxications AC is not recommended; note that this is phonetically similar to the word “Fails”.[23] The acronym stands for the following: P is for pesticides, petroleum distillates and unprotected airway. H is for hydrocarbons, heavy metals and time › 1h from ingestion. A is for acids, alkali, alcohols and altered level of consciousness with aspiration risk. I is for iron, ileus and intestinal obstruction. L stands for lithium and lack of gag reflex. Finally, S is for solvents and seizures.[23] A description of all the contraindications for AC are presented in section 5.

Posology for Single Dose of Activated Charcoal

The optimal dose of activated charcoal is unknown.[1] The adsorption can potentially become saturated and therefore with greater area available there is potentially more adsorbed substance.[2,10,24] The dose most commonly used is a 1:10 ratio of

Table 2. Recommendations for Use of Multiple Doses of Activated Charcoal.

Indicated	No support or exclude its use	Controversial	Not recommended
Where elimination was increased.	Studies in Volunteers that demonstrated increased elimination.	Studies are insufficient to recommend its use.	Studies have shown no increase in elimination.
Carbamazepine	Amitriptyline	Salicylates	Astemizole
Dapsone	Dextropropoxyphene		Chlorpropamide
Phenobarbital	Digitoxin		Doxepin
Quinine	Digoxin		Imipramine
Theophylline	Disopyramide		Meprobamate
	Nadolol		Methotrexate
	Phenylbutazone		Phenytoin
	Phenytoin		Sodium valproate
	Piroxicam		Tobramycin
	Sotalol		Vancomycin

Adapted from: American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists. Position Statement and Practice Guidelines on the Use of Multi-Dose Activated Charcoal in the Treatment of Acute Poisoning. Clin Toxicol (Phila). 1999;37(6):731-751. Copyright© 1999, Taylor & Francis.Reprinted with permission from Taylor & Francis.[38]

drug: charcoal.[2,12,24]

The United States Pharmacopeia (USP DI, 2003) recommended the following oral dosage regimen, which is the dosage recommended by the American Academy of Clinical Toxicology:

- Children up to the first year: 0.5 to 1 g per kg.1
- Children 1 to 12 years: 0.3 to 1 g per kg.1
- Adolescents and adults: 25 to 100 g, or 1 g per kg. The maximum dose is 50g-100g.1,10

Indications for Administration of Multiple Doses of Activated Charcoal.

Although the administration of multiple doses of activated charcoal has been shown to be beneficial in some cases and may enhance the elimination of a variety of drugs.[12,25-37] There is no published evidence supporting that administration of multiple doses of activated charcoal results in decreased morbidity or mortality in poisoned patients and therefore routine administration of multiple doses of activated charcoal is not recommended in the poisoned patient.

By administering more than two doses of activated charcoal it is believed that a concentration gradient is maintained in the gastrointestinal tract, and thus as drugs continuously pass through the intestinal bloodstream, these can potentially be absorbed back into the gut and onto the charcoal. This process to enhance elimination is known as "gastrointestinal dialysis".[12,17,39,40] A summary of the studies performed on AC's enhancement of drug clearance using multiple-dose activated charcoal has been performed and published elsewhere and exceeds the scope of this review.[41]

Gaudreault[12] suggests to consider administration of multiple doses of activated charcoal if any of the following criteria are met:

1. Intake exceeds the capacity to be adsorbed by a single dose.
2. It can prevent the reabsorption by enterohepatic circulation of the active substance, metabolite, or drug conjugate that is hydrolyzed by bacteria in the bowel.
3. Intoxication by drugs with sustained release.
4. Poisoning by drugs that decrease gastrointestinal transit (anticholinergics, tricyclic antidepressants, opioids, and phenothiazine).

The list of toxins on which clearance can potentially be increased with multiple doses of activated charcoal are described in Table 1.[12] In the position paper by the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists the recommendation is that administration of multiple doses of activated charcoal should be considered in intoxications where there has been a life threatening dose of carbamazepine, dapsone, phenobarbital, quinine, or theophylline ingested as this could potentially avoid the need for invasive extracorporeal techniques needed for treatment, but defer the ultimate decision on clinical judgement by the treating physician, presence of contraindications and effectiveness of other methods of treatment.[38] Their recommendations for use of multiple doses of activated charcoal are illustrated in Table 2.[38]

Posology for Multiple Doses of Activated Charcoal:

More studies are needed to identify the optimal dose for administration of multiple doses of activated charcoal.[38] The recommendation is to administer from 0.25 to 1 g / kg every 1-4 hours, when there is clinical evidence of absorption of the substance either by laboratory tests (increasing serum concentration) or known nature of the substance (sustained release formulations).[12] Doses of activated charcoal should be continued until the patient's condition improves by clinical and/or laboratory evidence.[12] One of the major limitations of multiple dosing is increasing nausea or emesis. This could be improved by administrating lower doses in shorter time intervals or continuous administration through a nasogastric tube. In some cases its necessary to initiate antiemetics.[12,38]

Contraindications

Contraindications to the Use of a Single Dose of Activated Charcoal

- Use in the setting of intoxication by substances not adsorbed by AC (see section 4.1)
- Substances that have a specific antidote: Administration of the antidote should be preferred because concurrent administration of activated charcoal with the antidote can reduce the effect of the antidote.[2,3]
- Non-intact gastrointestinal tract: Patients with anatomic or functional abnormalities of the gastrointestinal tract. For example, patients with intestinal obstruction.[1]
- Patient with an unprotected airway or with altered mental status without endotracheal intubation.[1,3,11,12] Consider that some patients can compromise their airway if the toxic agent is a central nervous system depressant.[2]
- If their use increases the risk of aspiration: For example poisoning by a hydrocarbon with high aspiration potential.[1-2,3,11]
- Pathologies, recent surgeries or medical conditions that increase the risk of gastrointestinal bleeding or perforation.[1-2,3]
- Use on intoxication by corrosive substances. It's not an absolute contraindication, can be considered if the dose and agent ingested can potentially cause systemic toxicity.[1,3]

Contraindications to the use of multiple doses of activated charcoal

The recommendations from the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists are listed below.[38]

Absolute contraindications to the use of MDAC are:

- An unconscious patient with an unprotected airway
- Presence of intestinal obstruction
- An injured gastrointestinal tract

Relative contraindications to the use of MDAC are:

- Decreased peristalsis

Consider that the patient has decreased peristalsis if there are decreased bowel sounds, abdominal distention or ileus. For example in cases of opioid overdose or anticholinergics. If activated charcoal is administered then the physician should monitor for gastrointestinal obstruction and prevention of aspiration.[38]

Use of Activated Charcoal in the Emergency Department

Initial management

When the patient arrives at the emergency room the initial resuscitation must be performed immediately. Evaluation of the intoxicated patient should start with initial supportive measures and management of the Circulation, Airway, Breathing (CAB's), a history and physical examination, toxidrome recognition, diagnostic testing and then start considering whether or not to administer decontamination measures, enhanced elimination measures or antidotes and consult toxicologists or regional poison control center. [42,5,43]

Subsequently, the physician should assess the risks, consider the possible clinical course and potential complications for the patient, as well as the risks and benefits of giving therapies to prevent absorption, increase elimination or indications for antidotes. Therefore, the decision to give a patient activated charcoal should be undertaken using the principles of evidence-based medicine where the clinician should make a value-based judgement on each individual patient.[14,44] Although there is little controlled trial evidence to support the administration of activated charcoal, the quantitative studies and evidence in small studies of select drugs suggest there is potential benefit in some situations and therefore it can have a significant role in an individual patient.[14,44]

Some authors suggest that the preferred method for gastrointestinal decontamination in awake patients with intact airway is AC.[5] For this process one must consider: the agent, dose, time from ingestion, current clinical presentation and individual patient factors. This process involves factors specific to the physician (experience, knowledge) and the patient (medical conditions, information provided).[3,45] Bailey proposed the decontamination triangle as a tool to help clinicians decide on administration of AC or not based on the potential toxicity of the poison, the benefit of AC, balanced against the risks of charcoal.[3,22] Activated charcoal or any other method of gastrointestinal decontamination should only be considered if there has been ingestion of a potentially toxic amount of substance that is severe and/or can threaten the patient's life and supportive management or antidotes may not be sufficient to ensure an optimal result. Some authors have recommended against use in mild to moderate intoxications.[11]

Administration of Activated Charcoal by Nasogastric Tube

The following description for administration of AC was adjusted from the "Protocol for Management of the Intoxicated Patient, Measures of Gastrointestinal Decontamination: Activated Charcoal" from the Hospital Universitario del Valle, in Cali, Colombia, written by JBV and Dr. Maurix Rojas, used with permission.

1. Put the patient in a comfortable position, preferably in sitting or left lateral position with the head at 450 angle and explain the procedure.
2. Isolate the airway with an endotracheal tube in patients with altered consciousness.
3. The size of the catheter will depend on the size and appearance of the patient: Adults can usually start with a 16 to 20 Fr catheter.
4. Measure the distance between the earlobe, the nasal apex and from there to the xiphoid to estimate the total length of the catheter that should be introduced.
5. Quickly and carefully insert the catheter in the nose. Lubricate the catheter with water prior to insertion.
6. Check that the catheter is in the stomach by flushing air with a syringe at the proximal end of the catheter and simultaneously auscultating on the epigastrium.
7. Secure the catheter to prevent movement during the procedure
8. Perform gastric lavage according to the existing protocol at your institution.
9. Prepare a solution of activated charcoal in a ratio of 1 gram of activated charcoal per 5 ml of distilled water (1:5).
10. Flush the catheter by administering 20 cc of distilled water or saline.

11. Dispense the total dose of activated charcoal with a 50 cc syringe through the catheter quickly.
12. Flush the catheter by administering 20 cc of distilled water or saline
13. Remove the nasogastric catheter immediately after the procedure.
14. Situate the patient in supine position with the head of bed elevated to 45°.
15. Record of the procedure in the medical record.

The clinical use of presentations of activated charcoal in tablets or capsules or super-activated charcoal is not recommended.[1,10]

Complications

Administration of activated charcoal is considered generally well tolerated, these are the reported adverse reactions and side effects.

- ***Aspiration:*** Some cases have been reported where patients aspirated gastric contents and the clinical picture has ranged from developing pneumonitis to rapid-onset adult respiratory distress syndrome and death.[11,46-48] A randomized clinical trial found equal rate of aspiration pneumonia among the group receiving supportive care and those who received activated charcoal.[20] While another large study of overdose patients looking at risk factors for aspiration pneumonitis did not identify activated charcoal as a risk factor.[46] Therefore the true effect is currently unknown.
- ***Emesis:*** Is generally considered an infrequent but the most common side effect.20 Reports have ranged from about 7% to 15% and even 25% of patients can have emesis although the trial by Cooper et al reported no difference in emesis when compared to patients who did not receive activated charcoal.[14,20,49]
- ***Taste:*** Ingestion of activated charcoal is reported to be distasteful to drink which may cause patient dissatisfaction.[14]
- ***Gastrointestinal obstruction:*** Has been reported mainly with use of multiple doses of activated charcoal but some studies have reported an incidence of 0%.48 In the literature there are 9 case reports of intestinal obstruction since 1981.[48]
- ***Constipation.*** More frequently observed with multiple doses.[1,38]
- ***Diarrhea.***[1]
- ***Gastrointestinal perforation:*** There have been a few cases reported with use of multiple dose activated charcoal or after nasogastric tube placement.[38,50]
- ***Electrolyte disturbances.*** Mainly related to use of multiple doses of activated charcoal. [38] One study found an incidence of hypernatremia 1: 176 patients (>155 mEq/L), and hypermagnesemia in 1: 292 patients (>3.75 mEq/L).[48]
- ***Death:*** Although very rare, in some case reports have found no cause of death from poisoning but activated charcoal.[1,38]

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Double Inlet Left Ventricle with Eisenmenger Syndrome in an Adult – A Case Report

Rahul Regi Abraham.[1,2]

Abstract

Background: Patient diagnosed with double inlet left ventricle (prevalent in 5 – 10 in 100,000 newborns) complicated with Eisenmenger syndrome had a median survival age of 14 years without corrective surgery. Congenital heart disease such as this is usually treated by multiple surgeries during early childhood. A surgically uncorrected case in adults is not of common occurrence. Further, generalized itching after coming in contact with water (aquagenic pruritis) presented an interesting conundrum to treat. **Case:** A 29-year-old patient in India presented at a primary health care center with a history of difficulty breathing and discoloration of extremities since birth. He also gave a history of itching which commonly occurred after taking bath, hemoptysis and history of turning blue in color after birth. Patient had received no treatment besides regular phlebotomies. On examination, there was grade IV clubbing and conjunctival congestion. Cardiovascular examination revealed an enlarged heart, heaving apex beat and a pan-systolic murmur. A provisional diagnosis of a congenital cyanotic heart disease was made. Investigations revealed hemoglobin of 16.8g/dl. X–ray and electrocardiogram showed hypertrophy of the ventricles. An echocardiogram showed double inlet left ventricle with L-malposed vessels but without pulmonary stenosis. A final diagnosis of congenital heart disease; double inlet left ventricle, L-malposed vessels without pulmonary stenosis, Eisenmenger Syndrome and absolute erythrocytosis was made. Patient was advised for further management with a cardiologist in a tertiary center but the patient did not follow up. **Conclusion:** Unlike in high-income countries where most congenital heart diseases are detected and dealt with at birth whereas low-and middle-income nations often have to deal with cases that present much later and should often be included in the differential diagnosis. Inability to follow up cases, centers that are poorly equipped and lack of facilities for investigations, patient's lack of medical awareness, and financial restrictions are major barriers to providing optimal treatment.

Keywords: Heart Defects, Congenital; Transposition of Great Vessels; Polycythemia; Eisenmenger syndrome; Pruritis (Source: MeSH-NLM).

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Introduction

Surviving adults with an uncorrected double inlet left ventricle (DILV) is not commonly seen[1,2]. Here we present one such case accompanied with Eisengmenger syndrome. DILV also known as "Single Ventricle" is a congenital heart defect where both the left and the right atrium opens into the left ventricle (Compare figure 1a. of normal heart and1b. of a heart with DILV). The right ventricle is either hypoplastic or does not exist. It has a prevalence of 5-10 in 100,000 new-borns [3]. DILV comprises about 1% of all congenital heart disease (CHD) 4. Median survival of surgically uncorrected patients is about 14 years [5]. Eisenmenger's syndrome (ES, Eisenmenger's reaction or tardive cyanosis) is a process by which the left-to-right shunt caused by a congenital heart defect in a foetus causes an increased flow through the pulmonary vasculature causing pulmonary hypertension [6] which over time causes increased pressure in the right side of the heart and reverses the shunt into a right-to-left shunt. An informed consent was taken from the patient for the purposes of this case report.

The Case

The patient is a 29-year-old male from India, born in rural Kerala, came to an NGO (primary level health care center, with free consultation) with chief complaints of breathlessness on exertion since many years and increased discoloration of fingers, tongue and limbs since the past 3-4 months.

- *Breathlessness:* Grade two (New York Heart Association classification) – Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea. Patient can walk for 0.5Km before the onset of dyspnoea. It is exaggerated on sustained physical activity and is relieved on rest. There was a progressive increase in breathlessness from the time of his birth till the patient was 10 years of age afterwards his symptoms have improved and currently shows no progressive increase.
- *Bluish discoloration of tips of fingers, tongue, lips:* It is present at all times. It increases on exposure to cold climates, exposure to cold water and other cold substances. This has been present since his childhood and is temporarily improved with phlebotomy.
- *Itching:* Started five years back. Gradual in onset. Non-progressive, continuous. Increases on taking a warm shower and relieved only after a phlebotomy.

No history of orthopnoea, paroxysmal nocturnal dyspnoea and platyopnoea, chest pain, palpitation, syncope nor edema.

He gives a history of a single episode of hemoptysis three years back which has not recurred since. Patient suffered from dengue when he was 18 years old and during laboratory investiga-

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Figure 1a. Normal Heart; 1. Understanding your child's heart - Double inlet ventricle (British Heart Association. 1st ed. 2016. Cited 28 November 2016. Available from: https://www.bhf.org.uk/publications/children-and-young-people/understanding-your-childs-heart---double-inlet-ventricle) Reprinted with permission from British Heart Association

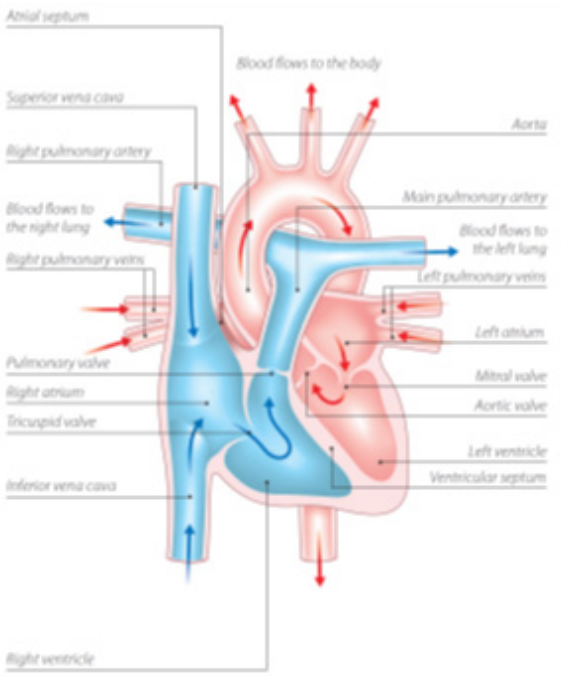
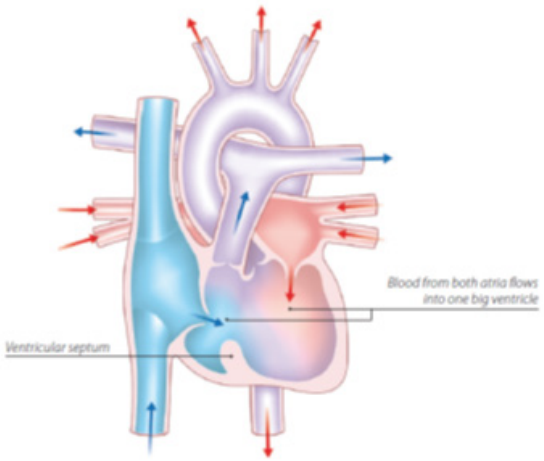


Figure 1b. Heart with Double Inlet Left Ventricle; Understanding your child's heart - Double inlet ventricle (British Heart association. 1st ed. 2016, cited 28 November 2016. Available from: https://www.bhf.org.uk/publications/children-and-young-people/understanding-your-childs-heart---double-inlet-ventricle). Reprinted with permission from British Heart Association



tion for the same he was found to have high hemoglobin levels and has since been asked to perform regular phlebotomies if his hemoglobin crossed 16g/dl (last phlebotomy in 2015). He gives history of difficulty gaining weight as a child and also history of repeated respiratory tract infections. There is no history of repeated throat infections, diabetes mellitus, hypertension, thyrotoxicosis or bronchial asthma. General examination revealed patient is moderately built and nourished (BMI: 18.51). Patient has red conjunctiva; clubbing (Grade IV); cyanosis of lips, fingers and tongue. His vital showed pulse: 92 beats per min, regular rhythm, normal in volume and character; Respiratory rate: 26 breaths/min, abdomino-thoracic respiration. Jugular venous pulse (JVP) was not raised.

Systemic examination

Cardiovascular System: Inspection (abnormal finding): Apex beat is visible in anterior axillary line in the 6th intercostal space. There are no dilated veins, scars or sinuses. *Palpation:* Position of apex beat is confirmed and is of heaving type. *Percussion:* Indicates an enlarged heart. Right border of the heart being percussed in right parasternal area. The upper border of the heart in the 3rd intercostal space in the parasternal line. The left border of the heart in the 4th intercostal space. *Auscultation:* S1 and a loud S2 heard. Pan systolic murmur heard at the apex. Loud p2. Examination of other systems reveals no abnormalities.

At this stage a provisional diagnoses of congenital cyanotic heart disease was made with the possible differential diagnosis being double inlet ventricle; Tetralogy of Fallot; patent foramen ovale; atrial septal defects; atrio-ventricular septal defects; ventricular septal defects, and the persistent arterial duct.

Investigations

A review of the patient's files the patient showed that the diagnosis of double inlet left ventricle was made at a tertiary level hospital but no therapeutic interventions were performed nor regular follow ups were made. Patient explained that financial difficulties, lack of awareness for the need for follow up and absence of symptoms that severely affected daily life were why he and his family did not feel the need for regular follow up. Additional exams revealed:

i. *Complete blood count:* Hemoglobin: 16.8 gm/dl; PCV:67.80 %; RBC:10.62 million/cu.mm
ii. *Chest Radiography (Figure 2)*: Cardiomegaly.
iii. *ECG:* Sinus tachycardia, bi-atrial enlargement; left ventricular hyper trophy; probable right ventricular hypertrophy
iv. *ECHO:* Left ventricle: Dominant; Right ventricle: Left outset; Great arteries are L-Malposed with Aorta to the anterior and left from RV; Pulmonary artery posterior and right from LV; Interventricular septum: Nonrestrictive bulboventricular foramen; Aorta arch: Left sided.

A final diagnosis of congenital heart disease; double inlet left ventrice, L-malposed vessels without pulmonary stenosis, Eisenmenger Syndrome and absolute erythrocytosis was made.

Management

The center at which the patient presented was not equipped neither with facilities to treat a cardiac case nor a cardiologist for consultation on further management strategies. The patient was counseled about the need for routine follow up treatment with a single doctor and was advice to visit a tertiary care center. Up to this day of writing this case report the patient has not visited a tertiary center and continues with occasional phlebotomies.

Discussion

Etiology

DILV to be genetically determined by multiple genes. Recurrence & transmission risks remain far below than that expected from medelian inheritance [7]. In the polygenic model, the phenotype is presumed to result from additive effects of multiple genes, interactions with other genes and environmental factors, and stochastic effects [8].

Pathophysiology

In a heart with DILV blood from both the atria flow into the left ventricles from here blood flows into the pulmonary circulation through the pulmonary artery and into the systemic circulation by shunting (left to right shunt) through the bulboventricular foramen and then entering the aorta (Figure 1b). The ratio of how much blood enters each circulation depends on the ratio of vascular resistances in the two vascular beds [8]. This results in a left to right shunt and later on its sequelae (Figure 3).

Prognosis

The actuarial survival rate without definitive repair was 57% at 1 year, 43% at 5 years, and 42% at 10 years for DILV. Moodie et al reported that 70% with well-formed single left ventricles died before age 16, with an annual attrition rate of 4.8% [15]. Usual causes of death are congenital heart disease, arrhythmias and sudden death from unknown causes. A10-year mortality rate among untreated patients approached 30-40% [16]. Common cause of death in these patients are hypoxemia and arrhythmia. They can also die from congestive cardiac failure, thromboembolism and massive hemoptysis.

Conclusion

Unlike high-income countries where most congenital heart diseases are detected and dealt with at birth low and middle-income nations often have to deal with cases that present much later and should often be included in the differential diagnosis.

In India there are far too many patients and too few doctors (Sudhir Anand, Victoria Fan. The health workforce in India, human resources for health observer series No.16. World Health Organization; 2016. Available from: http://www.who.int/hrh/resources/16058health_workforce_India.pdf. Accessed June 8, 2017. The World Bank. World development indicators: Health systems. Available from: http://wdi.worldbank.org/table/2.12#. Accessed June 8, 2017). Public health systems are overcrowded and private health care is expensive and is mostly set up in urban India as compared to rural areas. There does not exist a system in place for patient follow up after treatment or to ensure that a patient has followed up at a higher center. Most patients seek symptomatic treatment and once their acute episode has been controlled will insist on discharge despite incomplete treatment of the cause. If the doctor refuses symptomatic treatment the patient will simply move on to another doctor that is willing to do so, hence compromising the health system. Financial difficulties provide another major problem; expensive treatment, investigation and drugs assure lack of adherence to treatment or failure to visit a doctor until the patient is significantly crippled. The Government should upgrade primary health centers and increase the doctor – patient ratio and implement strategies for the effective utilization of the present doctors such as increasing the prominence of primary health centers thereby decreasing the load on tertiary centers, medicines and basic scans such as the echocardiogram should be more affordable. The process for improvement of health care in India has been initiated and will require many more years to reach a level that can be compared to high-income countries.

Figure 2. X-ray Chest Posteroanterior View Showing Cardiomegaly [(A+B)/C = 0.54, A= 3.28cm, B = 6.83cm, C = 18.52cm]

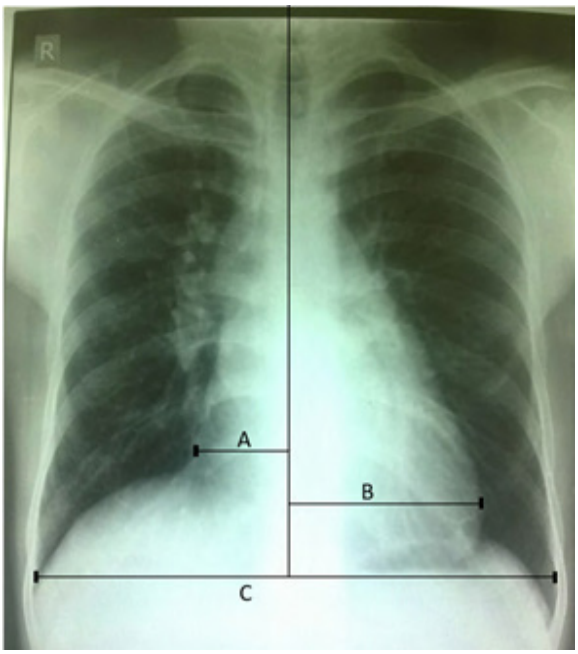
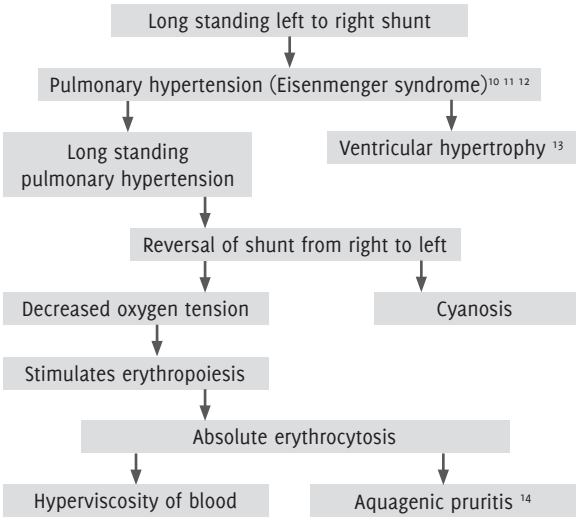


Figure 3. Sequelae of double inlet left ventricle.



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A Religious Patient and Her Sleep Problems: Reflections on an Experience in which Sleeping Pills were not Prescribed

Thiago Henrique Roza[1]

Abstract

The spirituality, cultural beliefs and religion of any patient are likely to have an impact on his/her health, and well-being. Health professionals, mainly young physicians and medical students, often fail to consider this type of background when taking care of their patients. This experience is a report of an interesting encounter, in the field of mental health, in which the spiritual beliefs and socioeconomic needs of a patient were considered during her treatment. Consequently, sleeping pills were not prescribed in her case.

Keywords: Spirituality, Mental Health, Beliefs (Source: MeSH-NLM).

About the Author: *Thiago Henrique Roza is currently a sixth-year medical student at Federal University of Parana, Curitiba, Brazil, of a six-year program.*

The Experience

Values, doctrines, and the beliefs that permeate any faith have an impact on the believer's mental health; usually, this impact tends to be positive for health and well-being.[1-2] However, in some cases, religion and spirituality represent a very difficult aspect of the patient's life, contributing to anxieties, worries, and sense of despair.[3] In addition, in several cases, mental health patients consider important to receive the support of a spiritual advisor, while trying to overcome the difficulties they are going through.4 Even though spirituality and religion have such a relevant impact, mental health professionals rarely consider this type of background when treating their patients.[5]

Some months ago, I was working in a public primary care clinic located in the city of Curitiba, Brazil. Unfortunately, considerable percentages of the patients of the clinic were vulnerable in socioeconomic terms.

The patient was a seventy-seven-year-old woman, who was asking for sleeping pills in order to sleep better. She mentioned that she was able to fall asleep every night around 9 PM; however, frequently, she would wake up two to three hours after going to bed, remaining awake until the day rises. Sometimes, she would wake up after a very bad dream. Usually, this nightmare was about her death and one-way trip to hell, to suffer for her eternity, all by herself.

During the medical interview, she told me her husband had left her for a much younger girl, when she was only forty-four years old. Abandoned, she had to raise her twelve children all by herself. Out of the twelve, only one remained with her, a forty-two-year-old male, with a diagnosis of paranoid schizophrenia. All the others had either died, or forgotten her with the busy ordinary activities of their daily lives. She was also financially broken, and on a delicate social situation, not having friends, or relatives she could count on.

As the interview went on, I tried to investigate her fear of going to hell, which seemed to be important for her, taking place in her mind and thoughts constantly, and appearing as recurring nightmares. She mentioned that she used to attend a Pentecostal church every week, but lately, she was feeling guilty for being so sinful, blaming herself for committing what she described as an unforgivable sin. She never read the bible, because she was illiterate; therefore, in her interpretation, she would never be able to enter the gates of heaven in the afterlife. She was always crying at night, thinking about how miserable she was for not being capable of reading the bible. Now, that she was an elder woman, she was fearing death and the possibility of not going to heaven, which for her was much worse than death.

Her illiteracy was not only a problem for her spirituality; she was also having troubles to control her blood pressure and glucose levels, as well to take her medicines correctly.

After a long talk to my supervisor, I convinced him that we should try a different approach for her treatment. With the help of other professionals of the clinic we enrolled her in a public elderly literacy program. We also taught her how to visually differentiate her pills, and the correct time for taking each one. I, myself, told her that illiteracy was not a sin, but a consequence of her difficult life history. For that consultation, we did not prescribe any medication.

In the city of Curitiba, there is a specific literacy program aimed for adults, run by the local Secretary of Health since 2002, which consists of literacy classes taking place in the primary care clinics. Usually, the teachers are volunteers, and the content of the classes are based on the daily lives and cultural values of the students. However, not all public clinics offer such a program (Available from: http://www.imap.curitiba.pr.gov.br/wp-content/uploads/2014/03/Revista_Gestao_Publica_em_

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Curtiba_Agos_2011.pdf, updated 2011, cited 2017 May 28). In this case, she was enrolled in an existing literacy class for adults, located on a public school near her home, which is part of a Brazilian educational program for adults' literacy (Available from: http://portal.mec.gov.br/index.php?option=com_docman&view=download&alias=8463-orientacoes-programa-brasil-alfabetizado-final-2011-pdf&category_slug=julho-2011-pdf&Itemid=30192 updated 2011, cited 2017 May 28).

Some weeks after, a colleague told me the follow up of that case. She, at that moment, was reading the first verses of her old bible. According to him, she was no longer suffering with nightmares, and having a much better sleep. At that moment she was much more hopeful about her future.

In conclusion, illiteracy is still a major problem for patients, mainly in low- and middle-income countries, representing important factor associated to mental health problems in such places. 6 Therefore, it is advisable for health professionals to be watchful about such a problem, and try to address it whenever possible. In addition, it is important to acknowledge and understand the religious and cultural background of the patients when taking care of them, because it may represent an important part of the treatment.

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Surprises in Applying and Interviewing at Residency Programs in the United States

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The Experience

I took a deep breath, closed my eyes and clicked on the submit button. Within a few seconds, my residency application was sent to a multitude of institutions across the United States. There were no congratulations, just a surprise credit card transaction pending my approval after the climax of submitting my application. There was a slight relief that evening but the anxiety of waiting for responses from programs came the very next day. Up until this point, preparing my residency application had been quite a stressful endeavour. Gathering letters of recommendation, writing my personal statement, and formatting my curriculum vitae all took substantial effort and time especially during intense summer electives. However, it all paid off when I started to receive interview invitations and I ran into a few surprises along the way.

My journey started in October with my first interview. The day began with some anxiety even though I had practiced answering standard questions such as "tell me about yourself" and "why this specialty?" with a classmate. Unexpectedly, by the third and fourth set of interviews, I felt very much at ease. Questions directed at me felt less like an interrogation and became more of a casual conversation. These discussions allowed me to discover more about the individual sitting across from me and also to learn more about the field I was going to spend the rest of my career in.

At most places, the interview day actually starts at the evening before with a pre-interview dinner with the residents. This was a great opportunity to meet the current residents and ask them about their experiences in the program. The actual interview day usually begins with a breakfast and introductory talk by the program director(s) and followed by several one-on-one faculty interviews. A tour or lunch would come next and sometimes a final wrap-up session to end the day. I was surprised at how difficult it would be to make a fully informed decision on a one-day visit but usually that's all the time we get. For the most part, I really considered my "gut" feeling after the interview day and whether or not I could see myself working with the residents and staff for the next four to five years.

I felt truly honoured to meet world-class physicians who are the leaders in their respective fields but yet astonishingly humble. I knew about them from a distance; I had read their papers, textbooks, and knew they produced hundreds of peer-reviewed journal articles. However, they were meeting and conversing with me like any one of their own colleagues. We spoke about a variety of topics, anything from their journey through medicine, their family life, to sharing their thoughts on the future of the specialty. I felt extremely lucky and touched that as a medical student I was able to get a chance to meet these leaders within the field.

One surprising aspect of my adventures through the residency interviews was meeting the other applicants. At first, I was anxious to meet the other applicants initially thinking that they were the type A personality, constantly comparing themselves to each other, while trying to edge each other out in a competitive environment. However, I found the opposite to be true. I have met some really friendly and remarkable individuals who really made me happy about my specialty choice. I may end up in the same training program as some of them and without a doubt run into them again at future national conferences or meetings. Ultimately, I would be working alongside these individuals in the future and I consider it an advantage that it was so amazingly easy to make friends with them all.

Another surprise during my travels was the cities that I thought had an undesirable reputation but upon visiting found them to be quite the opposite. Although I grew up in Canada not too far away from the US border, I always heard negative things about certain cities. For instance, Detroit was a great city to visit despite its notoriety for crime. There were certainly pockets of Detroit that felt uneasy (i.e. around the hospital) but then there were other areas where you would feel completely safe walking alone at night. Some other unexpectedly interesting cities were Cleveland (Ohio), Houston (Texas), and Baltimore (Maryland). I would suggest reserving an extra day or two to really explore these cities and see the sights outside of the hospital - you may be pleasantly surprised at what you discover.

Although I was offered many interviews, I was unable to accept and attend them all. In order to help me decide which places to select for an interview, I relied on several sources such as the "Student Doctor" forums, Doximity and current pathology staff and residents (1. Student Doctor Network Forums [Internet]. 2017 [cited 2017 April 16]. Available from: https://forums.studentdoctor.net/
2. Doximity [Internet]. 2017 [cited 2016 September 15]. Available from: https://www.doximity.com/). However, many

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of the comments and reviews from forums about programs are out of date and not entirely reliable. For the most part, I used Doximity as a guideline to ranking programs prior to interviews. Additional sources I used were faculty members and current residents. During my electives, speaking to the current first year interns really helped to get an impression of other programs as they had recently completed the interview season less than a year ago. In addition, faculty members offered a tremendous source of knowledge where I was able to gather information about the long-standing reputation of programs over many years.

It is important to mention that the National Resident Matching Program (NRMP) recommends that there has been a recent trend of an increasing length of the rank-order-list for applicants. The rank-order-list is the number of programs that an applicant is willing to place on their potential match list. In 2016, all matched applicants ranked 10.46 programs on average while US matched applicants ranked 11.97 programs (Impact of a Rank Order List. National Residency Matching Program, 2017 Available from: http://www.nrmp.org/wp-content/uploads/2016/05/Impact-of-Length-of-Rank-Order-List-on-Main-Residency-Match-Results.pdf. cited 2017 April 18). Thus, selecting and scheduling interviews were a daunting task but gathering information from several sources helped to make the process much easier. "Would you like to come back for a second look?" At the time, I was uncertain what that meant when I was first asked this question at the end of the interview day. A second look meant that I was able to come back and visit the program at another future date to explore and learn more about their daily practices. At this point, this was the program that I wanted to rank highly so I immediately said yes. The second look day was a very different experience from the interview day. I got a chance to attend conferences, observe many more resident/faculty interactions, and spend more time with the residents. I felt it was a very valuable experience and the visit confirmed my initial impressions to rank this program as my number one.

After completing my interview experiences, my recommendation to future applicants is to keep an open mind about everything that happens during the interview season. As you visit each program, you may "click" with certain faculty, residents, staff or program's philosophy. It is important to understand how each program may or may not fit to your own individual needs. Each applicant should sit down and reflect upon the things that they value most out of their residency training and try their best to match those goals with a potential residency program. By staying flexible, open, and honest about yourself, you may find some positive surprises in unexpected places.

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Why Did I Choose Pathology as a Career?

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The Experience

It seems that the majority of individuals stumble upon the field of pathology by chance. I was no exception to this rule. Since entering medical school, I thought that I was destined to become a surgeon. Fortunately, during my clinical clerkship years, the pathologists at our medical school had a major influence on the medical curriculum. There was to be a mandatory pathology rotation for four weeks and there was no escape. However, this experience generated the spark for my excitement to be entering into the field of pathology.

My first encounter with the field of pathology actually began a long time ago when I was doing research during my graduate studies. We had completed a seven month long project to try and detect a fluorescent compound crossing the blood brain barrier into the brain of a mouse. However, the imaging technique did not work and we were about to scrap the whole experiment. After several discussions, we concluded that histology would be the best way to salvage the work. I spent months analyzing histological slides of mouse brains to determine if the fluorescent agent made it in to where we wanted it to go. It worked and we were able to prove the function of the contrast agent using basic histology!

During medical school, my first exposure to pathology was in the second year pathology lectures. However, that was not the turning point for me to decide to enter the field. In the next year, I was randomly selected to undergo the mandatory pathology rotation. There was exposure to anatomical pathology, autopsy, clinical chemistry, microbiology, and molecular pathology. During anatomical pathology, we would observe resident's gross specimens and have our own set of unknown slides to go through. Autopsies were very involved and also interesting to work out what was the cause of death. Clinical chemistry was stimulating as the rotation allowed us to work up metabolic abnormalities and watch how residents dealt with inquiries from local family physicians and doctors in the main hospital. Microbiology and molecular pathology were much more laboratory based but it was a very scientific experience, for example, on how to logically reason out how to decipher which bacteria was to be tested based upon the clinical history.

After this rotation, I finally got a chance to observe what pathologists do on a daily basis and it completely changed my perspective. Although most pathologists do not deal directly with patients they have plenty of interpersonal interactions with laboratory staff, trainees, referring physicians, and medical students. I had the opportunity to be present at multi-disciplinary team meetings or tumour boards and the pathologist presents the diagnosis and describes the microscopic and macroscopic findings, which all directly drive patient care. It was at this moment that I realized how valuable information from pathologists were in helping other physicians determine what the next steps are in patient management. In some cases, the diagnosis given by pathologists will also dictate the potential treatment options available for patients.

After this enlightening experience, I decided to follow up and apply for electives in pathology. I did two weeks of anatomical pathology in Canada and a further four weeks in the United States. I had an opportunity to work with some world-class pathologists and I knew that this field was for me. I had a chance to work with some of the latest technologies such as laser micro-dissection, where I was acting as a pseudo-surgeon cutting out tumour cells from a several micron thick tissue section using a laser under the microscope.

However, not all of my experiences in choosing a career in pathology were all positive. After deciding and discussing with faculty, clinicians, residents, and medical students, most were completely surprised at my answer to "what do you want to specialize in after you graduate?" I received demeaning looks and given unhelpful comments such as "you must really hate dealing with people… have no clinical skills… no social skills… must be only interested in research". However, the most common remark was "you must love working with dead people". Every so often, I encountered compliments in disguise such as "but you're great with patients, I don't understand why you would want to go into pathology?" I understand that there is a particular type of stigma attached to this field but I take all of these various comments with a grain of salt. Deep down, I know that my work as a future pathologist will be making a difference in many living patients (unless I truly do decide to go into forensic pathology). I was extremely fortunate to meet several surgeons along my path who did truly understand the value of a pathologist and supported my decision to enter this field.

For comparison, in the 2017 National Resident Matching

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Program (NRMP), there were 1281 post-graduate year 1 (PGY-1) positions available for categorical surgery while 601 spots for pathology (National Resident Matching Program. Advance Data Tables: 2017 Main Residency Match, 2017. Available from: http://www.nrmp.org/wp-content/uploads/2017/03/Advance-Data-Tables-2017.pdf. cited 2017 April 16). However, only 35.9% of US graduates decided to enter pathology while 78.5% of US graduates matched to a general surgery program. There was a 2.1% decrease in the number of local graduates matching to a pathology residency program this year compared to 2016. However, this may have been explained by the decrease in number of US applicants and a subsequent increase in the number of PGY-1 pathology residency positions compared to last year's match results. In addition, medical schools do not actively promote pathology as a specialty career and many medical students will have never rotated through a pathology department. Thus, stereotypes about pathology come from within the profession such as: "pathologists didn't like people", "they had poor communication skills" or "they spent all day with dead bodies" (Schubert M. The last Respite of the Socially Inept? The Pathologist, 2017. Available from: https://thepathologist.com/issues/the-last-respite-of-the-socially-inept/the-last-respite-of-the-socially-inept/. cited 2017 April 16). Therefore, the overwhelming majority will unfortunately base their entire knowledge of the field upon negative stereotypes from outside and inside medicine.

However, I believe that the future of pathology is extremely bright. Laboratory testing with next generation sequencing allows us to scrutinize each patient's genome. I envision that pathologists will be able to give a diagnostic report to a clinician, for example a family physician, detailing the potential lifetime risks for cancers to guide the history and physical exam.1 This information can help determine what drug is most efficient based on the enzymatic makeup of a patient to determine which pharmacological therapies would be the most beneficial. Finally, we now know that every tumour is different and by analyzing the genetic makeup of a tumour we can determine whether it will respond to a particular chemotherapy.1 Although the term "personalized medicine" has been around for some time, it is only now that we can see the power of laboratory testing playing a more significant role in clinical medicine. The prospect of all this scientific and technological development makes me extremely excited to be entering this field. Even if you are determined to become a surgeon (like I was), I encourage all medical students to rotate through your local friendly pathology department to learn the importance of what we do and how we can help you take care of your patients better.

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