



JOURNAL OF THE PHILIPPINE MEDICAL ASSOCIATION

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June - December 2019

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Editorial Office:

2nd Floor PMA Building, North Avenue, Quezon City 1105 Philippines
Contact Numbers: +(632) 929-7361; +(632)929-6366; Fax: +(632) 929-6951
Website: www.philippinemedicalassociation.org;
E-mails: info@philippinemedicalassociation
philmedas@yahoo.com; philmedas@gmail.com

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MESSAGE



Warm greetings from the Philippine Medical Association!

This year's issue of the Journal of the Philippine Medical Association features the winning entries of the 2019 Resident's Research Competition, to include other papers that been thoroughly reviewed and carefully selected by the Committee on Publications. These were submitted by Filipino Resident physicians from various healthcare institutions, specialty organizations, medical schools and universities.

Research is an essential component academic advancement through evidence based medicine. This annual competition contributes to knowledge and expertise sharing consistent with the objectives of the Continuing Professional Development (CPD) Law or Republic Act 10912. The CPD Law aims to ensure that the Filipino physicians keeps pace with latest trends and internationally accepted standards of medical practice.

We thank the physicians who support and participate this annual competition, and recognize the effort that went into the preparation and presentation of these worthwhile research papers.

PMA trusts that this journal will be beneficial to all our physicians in strengthening their skills and knowledge to promote an even higher quality healthcare for all Filipinos especially during this time of pandemic.

JOSE P. SANTIAGO, JR., MD
President, Philippine Medical Association

Journal of the
Philippine Medical Association
Instruction for Authors

General Information

The Journal of the Philippine Medical Association (JPMA) is the official publication of the Philippine Medical Association (PMA).

The JPMA is published twice in a year at the PMA Office, 2nd Floor, PMA Building, North Avenue, Quezon City 1105, Philippines. It publishes original scientific papers pertinent to medicine and allied fields. It also considers for republications of previously published articles, either in their original or modified forms, provided they are accompanied by written permission from the publisher and principal author.

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Editorial Policies

The JPMA is a peer-review journal designed to meet the continuing education requirements of PMA members and the medical community. It adheres to the guidelines established by the International Community of Medical Journal Editors (ICMJE); however, for purposes of this issue, the previously circulated JPMA Instructions for Authors, although with some modifications, are still being followed.

Ethical Considerations

In the conduct and reporting of research, the JPMA adheres to the ethical considerations set forth by the ICMJE with respect to authorship and contributorship, editorship, peer review, conflicts of interest, right to privacy and confidentiality of patients, study participants as well as authors and reviewers; and, the protection of human subjects and animals in research.

All financial or personal relationships that could be viewed as presenting a potential conflict of interest must be disclosed by the author(s) and all participants in the review and publication process.

In experiments involving human subjects, authors must indicate in their reports whatever procedures are compliant with the standards of the responsible institutional and national committee on human experimentation as well as with the Helsinki Declaration of 1975, as revised in 2000. In case of doubts as to the procedures, authors must show proof of approval of their institutional review body or its equivalent.

In experiments involving animals, authors must indicate in their reports compliance with the institutional and national guide for laboratory animal experimentation.

Manuscript Preparation

(This section is primarily based on the previous and existing JPMA Instructions to Contributors but with some modifications based on the ICMJE recommendations. A completely revised version based on the guidelines of the ICMJE will be published in the next issue.

Accompanied by a cover letter from the principal author, the manuscripts, figures, tables, photographs, and references should be submitted in duplicate (an original and a copy) and typed double-space (including legends and footnotes) on one side of a white bond paper, 8.5 and 11 inches properly numbered consecutively on the upper right-hand corner of each page beginning with the title page. Illustrations must also be in duplicates. An electronic copy of the articles in a CD must be submitted.

The first page should contain the title, subtitle (if any, all authors' full names and highest earned academic degrees, and hospital or institutional affiliations. It must also include disclaimer, if any.

For the original article, an abstract must be type at the beginning of each paper after the title. It must contain, in structured format, the following: background or context of the study, objectives, methods, results and conclusions of the study, as appropriate. It must not be more than 300 words. No footnotes/references must be in the abstract. For other articles, an unstructured abstract may be preferred. Below the abstract, identify three to ten keywords or short phrases that will assist in indexers in cross-indexing the article.

Abbreviations and nomenclatures: the use of abbreviations should be minimized and preferably confined to tables only; non-standard abbreviations must be accompanied by legends.

Generic names of drugs are preferred. Trade names may be given only once at the end of the paper or in the acknowledgement and should follow the generic name in parenthesis.

References are to be cited consecutively in the text as superscripts numbers. At the end of each article, references should be listed consecutively in the numerical order as they appeared in the text

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Submission

Manuscripts, correspondence, and all materials for review and publication should be sent to the Editor-in-Chief of the Journal of Philippine Medical Association at the Editorial Office.

Subscription and advertisements, including change of address should be sent to the PMA Secretariat at 2nd floor PMA Building, North Avenue, Quezon City, 1105 Philippines.

Validation Study of a Psoriasis Registry Questionnaire*

Paola Andrea Lorenzo, MD¹

ABSTRACT

Introduction. Psoriasis affects 0.1-3% of the world's population. It is a chronic multifactorial disease with a genetic basis and various triggering factors. In the Philippines, extrapolated data from 2004 reveals a 2% prevalence. Thus it is important to develop a database with psoriasis patients' demographics, disease characteristics, treatment and quality of life.

Most institutions still rely on paper-based methods of recording patient data. This is prone to error and destruction. Further consolidation and analysis of this unsystematic data is problematic, making it difficult to assess real-time setbacks and develop programs.

Objective: To develop and assess the validity of a Psoriasis Questionnaire in the local setting, which will be further utilized towards developing a Psoriasis Registry. The data from this can in turn be used to generate a Psoriasis Guideline.

Methods: This is a multicenter study. The Questionnaire was developed from Psoriasis literature and worldwide registries, as well as local patient encounters. It was answered by Dermatologists and their patients. Cronbach's alpha (CA) was used to check for validity and internal consistency of the questionnaire.

Results & Conclusion: 124 questionnaires were accomplished. Each part of the questionnaire was assessed with CA. Some sections showed CA <0.70, indicating variability in the test response. To improve this, some modifications in the Questionnaire were recommended. The overall CA score however was 0.8, indicating that in totem the questionnaire is consistent and valid.

Keywords: Psoriasis Registry, Philippines, Psoriasis Questionnaire

*1st Place, 2019 Philippine Medical Association Original Research Presentation Contest, May 15, 2019

¹Resident, Victoriano Luna Medical Center, Quezon City

INTRODUCTION

Psoriasis is a universal skin disease affecting as much as 0.1-3.0% of the world's population. It is a chronic multifactorial disorder with a genetic basis, and various triggering factors¹. Patients suffer greater morbidity and mortality not only due to cutaneous manifestations but to systemic disorders as well. Augustin et al. found that metabolic syndrome was 2.9 times more frequent among patients with psoriasis², and Lee, M.S., et al. elicited that psoriasis patients had a higher risk of mortality from malignancies and circulatory system diseases as compared to the general population³. Overall, these factors may lead to significant impairment of a person's quality of life. Different treatment modalities are available for psoriasis, treatment however should be patient-specific. It is therefore important to note disease severity, co-morbidities and patient preference in selecting a treatment regimen. Tapia et al. pointed out the need for "shared decision-making" between the physician and patient in order to achieve treatment satisfaction. The study reveals that more than half of patients were "dissatisfied" with their treatment regimen, being directly related to not receiving enough options⁴.

Philippines extrapolated data from 2004 reveals a 2% prevalence of psoriasis⁵. Due to such, it is important to develop a psoriasis database containing the patients' demographics & lifestyle, disease' clinical presentation & progression, treatments, and the subsequent quality of life. Most of our health care institutions still rely on paper-based methods of recording patient data and information. This is often prone to error and destruction. Further consolidation and analysis of this unsystematic data is problematic, rendering our health-care professionals and policy makers at a disadvantage in developing the best treatment strategies and policies. Therefore the purpose of this study is to validate a questionnaire answered by dermatologists and their psoriasis patients, which may be later be used as a basis for a Psoriasis Registry in the country. Having a Philippine Psoriasis Registry will be of great value to patients, physicians, policymakers and government agencies. It may be used to further develop clinical practice guidelines for Psoriasis in the local setting and aid law-makers in building programs for this particular group. Moreover, data gathered will be

valuable in the field of research and study of Psoriasis, specifically impacting advise, management and treatment of our patients.

Methods

Trial Design

This multicenter Questionnaire validation study were filled-up by Philippine Dermatologic Society (PDS) - accredited dermatologists or supervised dermatology resident physicians, and his/her psoriasis patients. The Dermatologists and the patients who participated came from ten different government/private hospitals and private clinics⁶. Permission to conduct the questionnaire was obtained from the Chairmen of the different participating hospitals and clinics. Each participating patient and dermatologist was given an Information Sheet and Consent Form for them to sign, indicating their willingness to participate.

The Questionnaire was developed from various literature and Psoriasis registries available worldwide as well as patient encounters in the local setting. It was formulated in a clear and concise manner, that the responders will simply tick boxes corresponding to their answers. The Study Adviser, who is a Psoriasis expert further reviewed this. The questionnaire (Appendix A) consisted of five parts – 1) Informed Consent 2) Demographic Data Sheet 3) Phototyping Asian Light to Darker Brown Skin⁷ 4) Psoriasis Data Sheet and 5) Psoriasis Lesion Score.^{8, 9, 10, 11, 12, 13, 14, 15}

The questions chosen were reflective of Psoriasis particularly in people of brown skin, living in the tropics.

Participants

The study participants were required to meet all of the following inclusion criteria:

- Patient is either Male or Female, 0 years old and above, a psoriasis- diagnosed patient - clinically by a PDS accredited dermatologist or resident dermatologist, or a biopsy-proven case.

- Consent form was understood and signed by the Psoriasis diagnosed adult patient or by the legal guardian of a minor patient (less than 18 years old upon answering the questionnaire).
- The dermatologist and patient were willing to participate in the study.¹¹

The following were used as exclusion criteria for the study:

- Individual who refused to give consent for the study.

Prior to answering the questionnaires, the investigators explained to the participating dermatologists, the process of answering the questionnaire. Each section of the questionnaire was thoroughly described.

The investigators addressed all questions & problems raised by the participants via e-mail or text message.

Sample Size

Cronbach's coefficient alpha is used as a measure for validity and internal consistency of measurement instruments such as questionnaires and scales. Based from the study by Yurdugul, H. "Minimum sample size for Cronbach's Coefficient alpha: A Monte Carlo Study", it states that if the value of the first eigenvalue obtained from principal component analysis (PCA) of the sample data set is higher than 6.00, the sample for coefficient alpha, even when $n=30$, is an especially robust estimator of the population coefficient alpha¹⁶. For this study, the first eigenvalue is set at 7.00, therefore a minimum sample size of thirty (30 different dermatologists, with their corresponding psoriasis patients) is set.

Safety and Ethical Considerations

The study meticulously followed the ethical principles stated in the Declaration of Helsinki and the National Guidelines for Biomedical/ Behavioral Research of the National Ethics Committee (NEC) of the Philippines.

The protocol has undergone review process of the Institutional Review Board (IRB) and was approved. There were no reported disparities from the approved protocol to the Institutional Review Board.

Study subjects were given clear and complete information and instructions about the study. There were no participants who withdrew during the entire data gathering. The researchers addressed queries or clarifications made by the dermatologists or patients. Study participants did not receive any material or monetary forms of payment but were provided with high-standard individualized medical attention and treatment.

All participants who were included in the study were advised on the study protocol. The participants signed the Informed Consent Form (Appendix A), as they have understood and voiced out their willingness to join the study.

Statistical analyses

Cronbach's Alpha (CA) was used to check for internal consistency of the Questionnaire. This is a measure of the correlation between each of the questions in the domains. A Cronbach Alpha value of at least 0.70 was considered an acceptable and reliable indicator of internal consistency at the group level.

Demographic data was summarized using means and standard deviation for quantitative data such as age, and frequency and proportion for qualitative data such as gender.

Results & Discussion

A total of 124 questionnaires were accomplished from December 2017 – July 2018.

The specific parts of the questionnaire garnered CA scores as follows:

Questionnaire Domain	Cronbach's alpha
Family history	0.38
Personal and social history	0.48
Psoriasis profile	0.72
Aggravating factors	0.46
Unmet needs	0.93

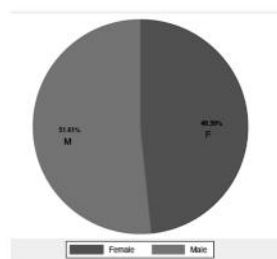
Total Questionnaire CA Overall : 0.8

As indicated by the CA scores per section, some are less than 0.70, this indicates variability in the test response, which may be due to measurement error because the number of categories per item varies, and there are some items with more than one answer. To improve the Cronbach alpha score, we may need to modify the Questionnaire choices by decreasing the number of possible answers or using a "Yes or No" answer – tick-box.

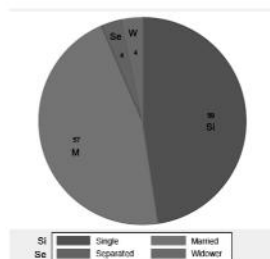
Overall however, the questionnaire garnered a Cronbach alpha score of 0.8 indicating that in totum the questionnaire is consistent and valid and may be used in a larger population to gather necessary data.

The following demographic data were gathered from our patient responders:

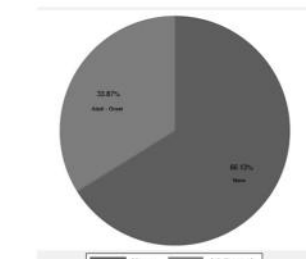
Most of our patients were male (51.6%), with a mean age of 43 years old (± 16.87 years old), single (57.6%), of Malay ethnicity (95.1%), and of the phototype IV (66%).



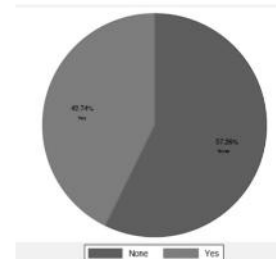
Gender



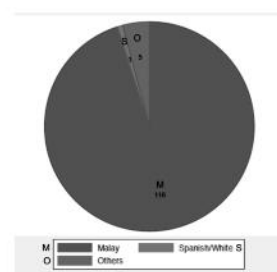
Civil Status



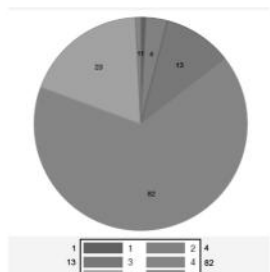
Family History of Diabetes



Family History of Hypertension

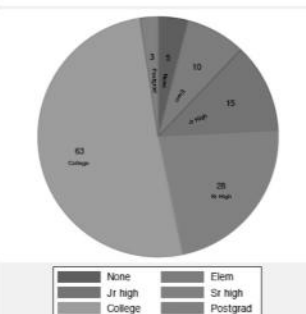


Ethnicity

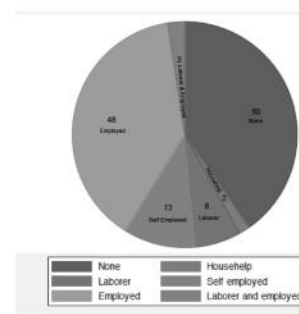


Phototype

From the Personal and Social History most of our responders where college graduates (50.8%) & employed (59.7%). Exercise (23.4%) was their most common form of physical activity

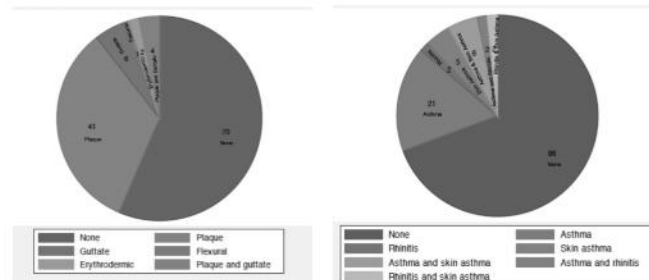


Education



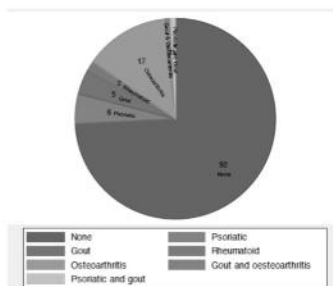
Work

From our interview of Family history, 56.5% denied a history of psoriasis, 69.4% denied that of atopy, 74.2% denied any forms of arthritis, 91.1% denied any other dermatoses, 66.1% denied a history of Diabetes and 57.3% denied Hypertension.

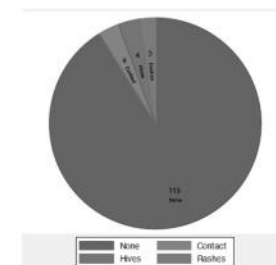


Family History of Psoriasis

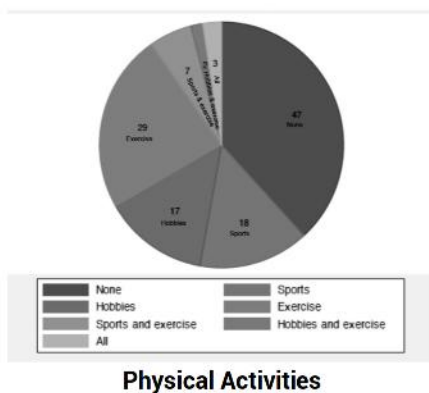
Family History of Atopy



Family History of Arthritis

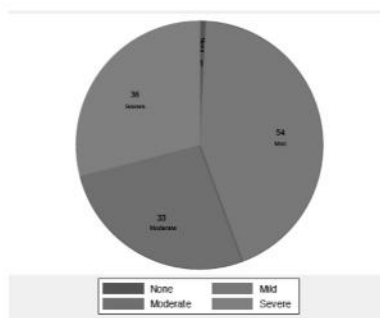


Family History of other Dermatoses



Physical Activities

From the Psoriasis Profile, most of the patients (43.6%) had mild involvement of the body surface area at the time of interview. Moreover we can note that most patients presented with mild erythema, induration and scaling of the head & neck, and upper & lower extremities. Exception is seen for the erythema, induration and scaling of the trunk noted to be moderate, as well as the erythema of the lower limb.

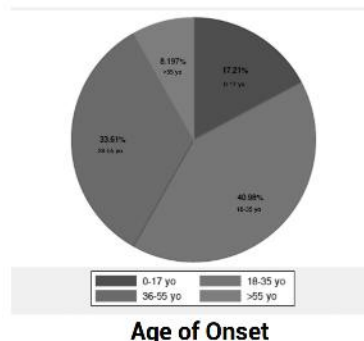


Severity of Psoriasis

Psoriasis Lesion Score

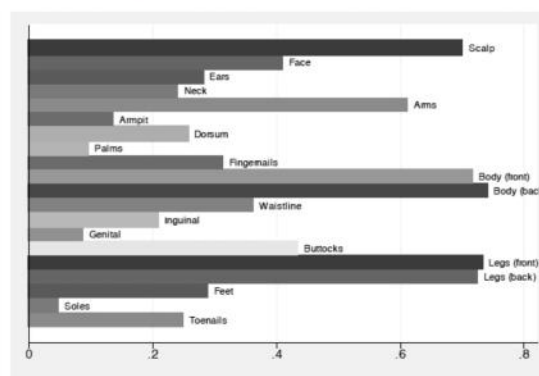
	Mean	Standard deviation	Median
Head & neck Erythema	1.11	1.09	1
Head & neck Induration	0.92	0.92	1
Head & neck Scaling	0.94	1.00	1
Upper limb Erythema	1.24	1.12	1
Upper limb Induration	1.06	0.93	1
Upper limb Scaling	1.06	1.03	1
Trunk Erythema	1.60	1.18	2
Trunk Induration	1.45	1.07	2
Trunk Scaling	1.38	1.11	1
Lower limb Erythema	1.63	1.19	2
Lower limb Induration	1.43	1.02	1
Lower limb Scaling	1.31	1.00	1

Majority of the patients recalled the age of onset of their psoriasis to be in the 18-35 year-old age-range (41.0%), and most had previous (71.5%) & current (75.6%) lesions of the plaque type.



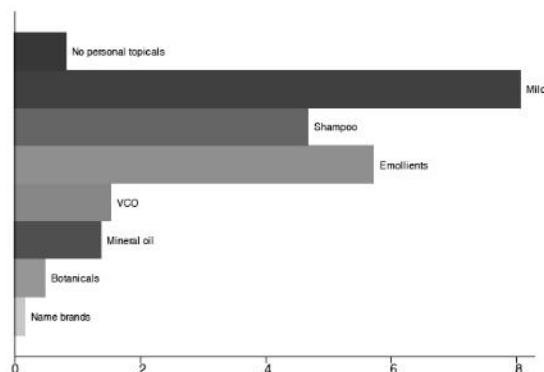
Age of Onset

The five most common affected areas were namely the back of the trunk (74%), the front (73%) & back (73%) of the legs, the anterior trunk (72%) and the scalp (70%).

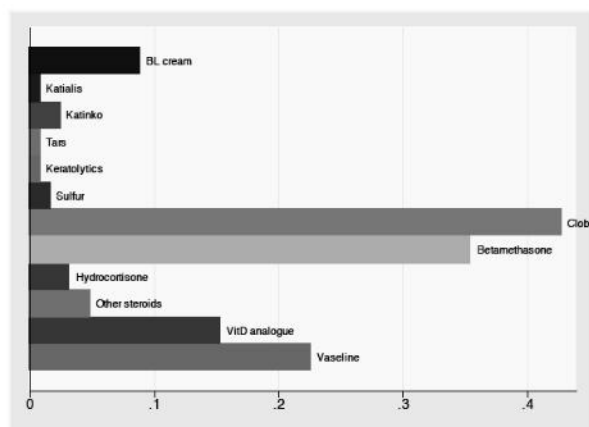


Affected Areas

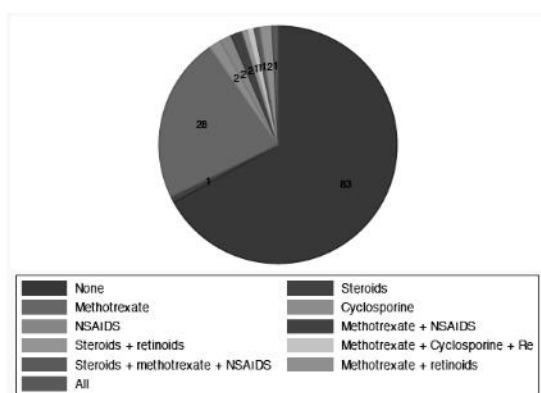
Our patients were noted to be using mild soap (81%), emollients (57%), virgin coconut oil (15%) and other botanicals (5%). Most of them reported using Clobetasol (43%) & Betamethasone (35%) as their active topicals. Some were taking oral drugs such as methotrexate (22.6%) and undergoing phototherapy (19.4%).



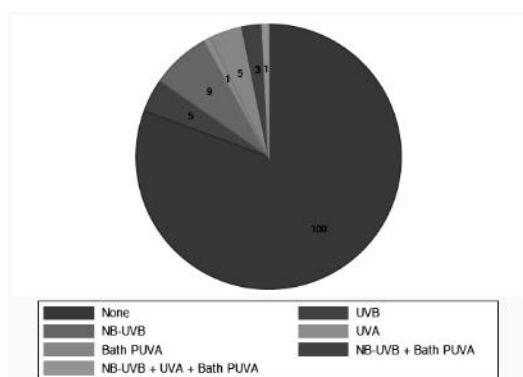
Personal Topicals



Active Topicals

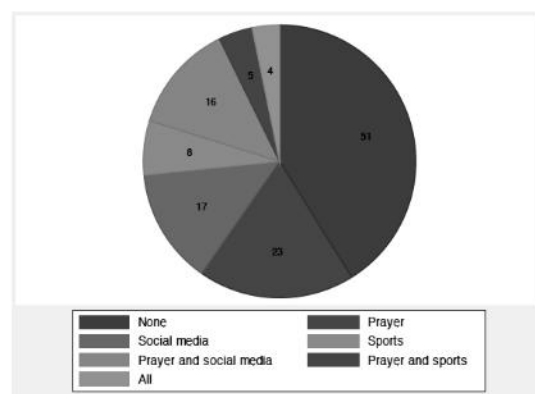


Oral Drugs



Phototherapy

As for modes of relaxation, interviewees sought prayer/meditation (18.6%), and social media (13.7%).



Mode of Relaxations

Only 8.9% of the interviewed patients had undergone treatment with biologics, with the most common drug used being Secukinumab (7.3%). Of these they reported clearing of the psoriasis lesions. Administration of the drug was mostly per protocol, although 1 patient reported administration upon disease relapse and 3 patients based it upon fund availability. Of those treated, relapse of lesions was most commonly noted after 1-2 months. Most patients utilized personal savings (21.0%) in funding their Biologics.

Biologics	Frequency	Percent
None	113	91.13
Ustekinumab	2	1.61
Secukinumab	6	4.84
Ustekinumab + Secukinumab	3	2.42
Total	124	100

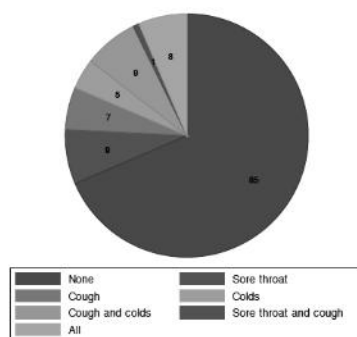
Response	Frequency	Percent
None	112	90.32
Clear/ mostly clear	11	8.87
Same	1	0.81
Total	124	100

Administration	Frequency	Percent
None	104	83.87
Per protocol	16	12.90
On relapse only	1	0.81
On fund availability	3	2.42
Total	124	100

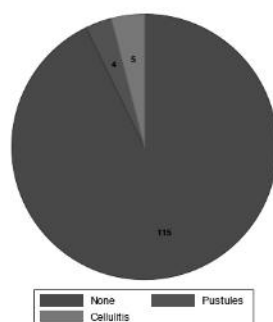
Only after	Frequency	Percent
None	109	87.90
<1 month	2	1.61
1-2 months	8	6.45
3-4 months	3	2.42
5-6 months	2	1.61
Total	124	100

Funding	Frequency	Percent
None	78	62.90
Savings	26	20.97
Donor	1	0.81
PWD	3	2.42
PCSO	2	1.61
Study	1	0.81
Others	4	3.23
Savings + PWD	2	1.61
Savings + PCSO	2	1.61
PWD + Philhealth	1	0.81
Savings + PWD + Study	1	0.81
Savings + PWD + Philhealth	1	0.81
Savings + Donor + PWD + Study	2	1.61
Total	124	100

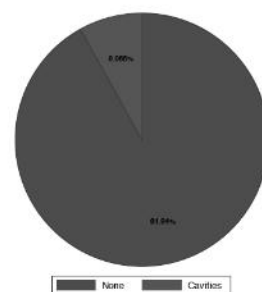
Of the perceived Psoriasis triggers, 31.45% associated a pulmonary cause to a psoriasis flare, 7.26% to a skin infection, 8.06% to dental cavities and 4.84% to urinary tract infection. This reflects our patient's understanding of their disease and what causes their "flares".



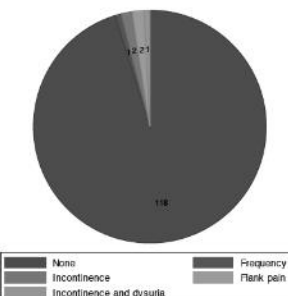
Pulmonary



Skin



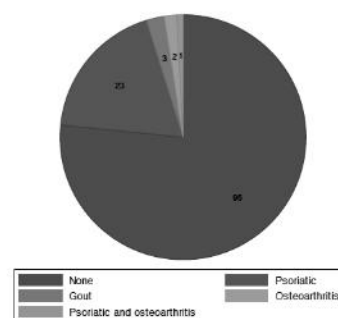
Dental



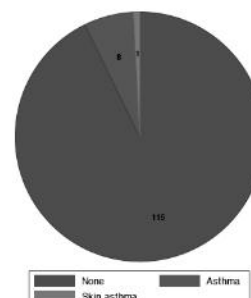
Urinary Tract

From the past medical history, 23.4% of our patients reported a concomitant psoriatic arthritis, and 7.26% had atopy. 95.97% denied other dermatoses & 98.39% denied any form of hepatitis

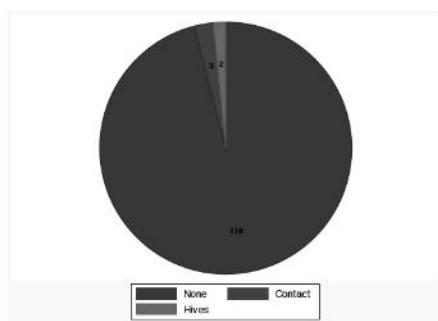
Other illnesses were as follows: 13.7% had hypertension, 6.5% were obese, 7.3% had atopy, 8.9% diabetes, 5% dyslipidemia.



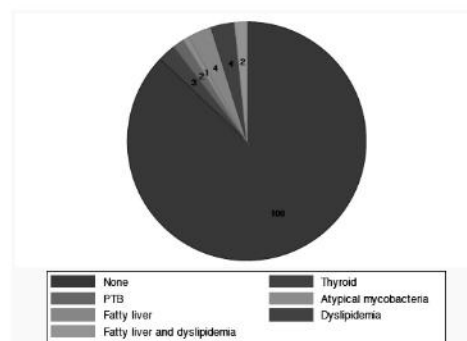
Arthritis



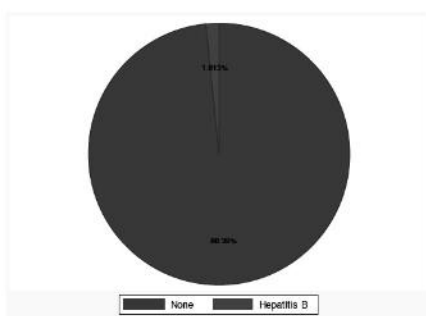
Atopy



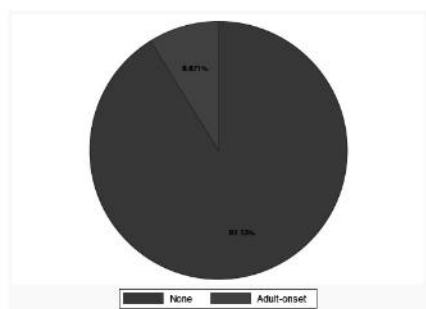
Other Dermatoses



Others

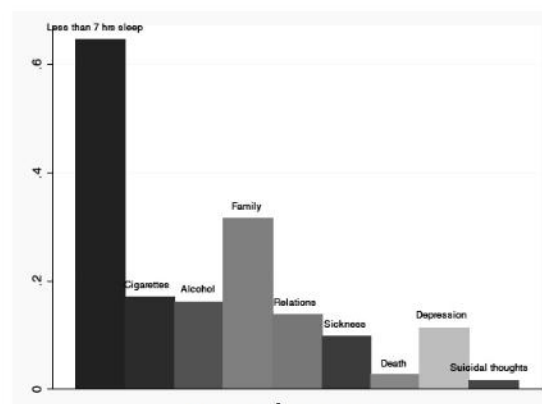


Hepatitis



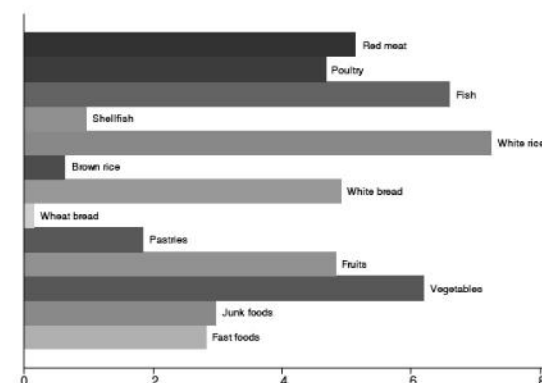
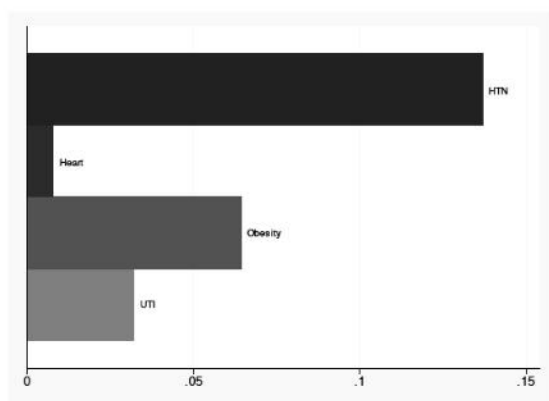
Diabetes Mellitus

Of the personal stressors, 65% pointed out lack of sleep as the most significant cause. 17% of the patients admitted to smoking cigarettes and 16% to drinking alcohol despite having psoriasis. 31% pointed out to family problems as their cause of stress.

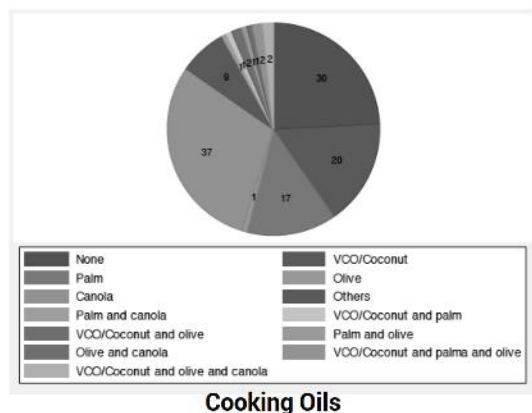


Personal Stressors

Assessing our patient's diet, we saw that majority were choosing the healthier options. More people chose to eat fish over red meat, and fruits & vegetables over pastries and junk foods. As a rice-loving country though, our patients favored white rice (73%) over brown rice (6%). As for the cooking oil, 30.0% were using canola oil, 16.1% used coconut oil and 13.7% used palm oil.



Usual Food Choices



The last part of our questionnaire tackled the unmet needs of our patients and the data is as follows: 86% were satisfied with their dermatologist based on the management, the time given to each patient, the explanation of the disease, the needed lifestyle changes and the different treatment options. 3% was not satisfied with his/her dermatologist and a remaining 11% had no comment.

As for the Rheumatologist, 82% of our patients were not seeing this type of doctor. 16% who were seeing the doctor reported to be satisfied and 5% were not satisfied.

For the Government support, most answered "None or N/A" because they were not aware of how the government was helping people with Psoriasis.

As for the distribution of the medications, 24% were happy with how the medicine was made available through their respective doctors. 27% however were not satisfied with the pharmaceutical companies due to drug cost

	N/A Frequency (%)	Satisfied Frequency (%)	Not satisfied Frequency (%)
Dermatologist			
Management	14 (11%)	107 (85%)	3 (2%)
Time spent	14 (11%)	106 (85%)	4 (3%)
Explanation	14 (11%)	107 (85%)	3 (2%)
Rheumatologist			
Management	102 (82%)	16 (13%)	6 (5%)
Time spent	102 (82%)	16 (13%)	6 (5%)
Explanation	102 (82%)	16 (13%)	6 (5%)
Government support			
Formulary	69 (56%)	27 (22%)	28 (22%)
Philhealth	77 (62%)	18 (15%)	29 (23%)
PCSO support	78 (63%)	14 (11%)	32 (26%)
MD-initiated research funds	77 (62%)	16 (13%)	31 (25%)
Distribution			
Direct to MDs only	68 (55%)	30 (24%)	26 (21%)
Instruction thorough	78 (63%)	21 (17%)	25 (20%)
Packaging secure	100 (81%)	6 (5%)	18 (14%)
Pharma Co.			
Support for research	78 (63%)	16 (13%)	30 (24%)
Decrease drug costs	80 (65%)	10 (8%)	34 (27%)

As you can see the data gathered is quite valuable as it reflects Psoriasis in Filipino skin. From this available data, we may better understand our patients and optimize their management and well-being. This may also lead to the development of different Psoriasis guidelines of care as well as Government and NGU (non-government unit) involvement programs for our patients.

Safety Considerations and Follow-up

This study is for the validation of a questionnaire on Psoriasis, which was distributed to the involved parties. A good clinical practice (GCP)-certified research staff acted as an Administrator of this study, for which patient privacy was safeguarded by assigning control numbers & securely storing pertinent information. The researchers do not foresee and found no significant adverse effects resulting from this study.

Recommendation

The Psoriasis Questionnaire was only distributed to willing participants in Metro Manila. The researchers recommend that for further studies, questionnaires will also be distributed to the different regions of the Philippines to be able to acquire a more representative population of the Filipino people.

Next, as stated above, some domains of the questionnaire have Cronbach Alpha scores of less than 0.70. Our statistician suggested that to improve CA, we need to modify the questionnaire by decreasing the number of choices and making it as objective as possible by eliciting answers such as Yes or No, by ticking a box as such:

For the Affected Areas section: Does your patient have affection on the following areas? Please put a check if YES or NO.

Areas Affected	Yes	No
Scalp		
Face		
Ears		
Neck		
Arms		
Armpit		
Dorsum		
Palms		
Fingernails		
Body front		
Body back		
Waistline		
Inguinal		
Genital		
Buttocks		
Legs front		
Legs back		
Feet		
Soles		
Toenails		

For the Personal Topicals section: Does your patient use any of the following? Please put a check if YES or NO.

Personal Topicals	Yes	No
No personal topicals		
Mild soap		
Shampoo		
Emollients		
Virgin coconut oil		
Mineral oil		
Botanicals		
Name brands		

For the Active Topicals section: Does your patient use any of the following? Please put a check if YES or NO.

Active Topicals	Yes	No
No active topicals		
BL cream		
Katialis		
Katinko		
Tar		
Keratolytic		
Sulfur		
Clobetasol		
Betamethasone		
Hydrocortisone		
Other steroids		
Vitamin D analogues		
Vaseline/ Petroleum jelly		

For the Personal Stress section: Does your patient consider any of the following as his/her source of stress? Please put a check if YES or NO.

Personal Stress	Yes	No
Less than 7 hours sleep		
Cigarettes		
Alcohol		
Family		
Relations		
Sickness		
Death		
Depression		
Suicidal thoughts		

For the usual food choices section: Are any of the following part of your patient's usual diet? Please put a check if YES or NO.

Usual food choices	YES	NO
Red meat		
Poultry		
Fish		
Shellfish		
White rice		
Brown rice		
White bread		
Wheat bread		
Pastries		
Fruits		
Vegetables		
Junk food		
Fast food		

APPENDIX A

Informed Consent and Questionnaire Form

PSORIASIS QUESTIONNAIRE VALIDATION STUDY (PQVS)

For the Dermatologist and the Psoriasis Patient: Please read the INFORMED CONSENT FORM below and the Questionnaire Pages that follow.

For any questions, anytime, please call Dr. Paola Lorenzo @ 0917 8823531 or
Dr. VMVerallo-Rowell @ 0917 8373134 or 8112449

INFORMED CONSENT

FOR THE DERMATOLOGIST	FOR THE PATIENT
I have read the information regarding the Psoriasis Questionnaire Validation Study (PQVS)	Nabasa at naunawaan ko ang lahat ng impormasyon at/o nakapagtanong ako ukol sa mga ito at wastong nasagot. Kusang loob akong sumasali sa pag-aaral na ito. Sumasang-ayon ako na maitala ang aking mga kasagutan at kuhanan ng litrato and katawan na tanging panloob (panty & bra) lamang ang kasuotan. Binibigyan ko ng pahintulot ang mga tagapagsaliksik na gamitin ang aking mga sagot at mga litrato para sa patuloy na pagsasaliksik ng mga Manggagamot ng Pilipinas sa ikauunlad ng kaalaman patungkol sa psoriasis.
I understand the study and/or have asked questions that were answered to my satisfaction	
I voluntarily consent to join in the PQVS	
Once you both agree, both Dermatologist and Patient – please sign and date in the presence of a witness.	
Dermatologist : Name in print, Sign & Date Patient: Name in print, Sign & Date Witness : Name in print, Sign & Date	

Page 1

PSORIASIS QUESTIONNAIRE DEMOGRAPHIC DATA SHEET

ID#

Name: _____ Age: _____

Sex: ☐ Female ☐ MaleCivil Status: ☐ Single ☐ Married ☐ Separated ☐ Widow/WidowerEthnicity: ☐ Malay
☐ Mixed: ☐ % Spanish/White ☐ % Japanese/Chinese/Korean
☐ % Indian ☐ % Other
COMMENTS

Place here any suggestions/comments that can further improve this Questionnaire

PHOTOTYPING ASIAN LIGHT TO DARKER BROWN SKIN

PHOTO TYPE	HISTORY		SKIN COLORS	
	Sun Burn & Tan	Pigment Darkening Change		Baseline: Of Buttocks
		<i>Immediate</i>	<i>Persistent</i>	
	Column 1	Column 2	Column 3	Column 4
I	Burn easy; Tan never	None (-)	None (-)	Ivory white
II	Burn easy; Tan hardly	Weak (±) to (± to +)	Weak (±+) to to very mild	White to Yellowish White
III	Burn & Tan moderate	Definite +	Mild +	White - Light brown
IV	Burn mild Tan easy	Moderate ++	Moderate ++	Beige-olive Light Brown
V	Burn rare, Tan dark	Dark Brown +++	Dark Brown +++	Moderate Brown
VI	Burn never Tan profuse	Intense Brown ++++	Intense brown ++++	Dark Brown To Black

Page 3

Source: Verallo-Rowell, V.M. (2001). *Multi-Heritage Asian-Filipino Phototypes adapted from Fitzpatrick in VMVerallo-Rowell, MD. Skin in the tropics: Sunscreens & hyperpigmentations. Anvil. Phil: 2001: 143-156*

FAMILY HISTORY	Psoriasis ☐ None ☐ Plaque ☐ Guttate ☐ Flexural ☐ Erythrodermic ☐ Pustular ☐ Palmoplantar		Atopy ☐ Asthma ☐ Rhinitis ☐ Skin Asthma		Arthritis ☐ None ☐ Psoriatic ☐ Gout ☐ Rheumatoid ☐ Osteoarthritis		Other Dermatoses ☐ None ☐ Contact ☐ Hives ☐ Rashes ☐ Blisters		Diabetes ☐ None ☐ Juvenile ☐ Adult ☐ High BP ☐ None			
	Education ☐ None ☐ Elem ☐ Jr High		☐ Sr High ☐ College ☐ MD/Masters/ PHD		Work ☐ None ☐ Home help ☐ Laborer		☐ Self-employed ☐ Employed		Physical Activities ☐ None ☐ Sports ☐ Hobbies ☐ Exercise			
PSORIASIS PROFILE	Severity ☐ Mild (<5% BSA) ☐ Moderate (5-10% BSA) ☐ Severe (≥10%)		Age of Onset ☐ 0-17 yo ☐ 18-35 yo ☐ 36-55 yo ☐ >55 yo		Previous Lesions ☐ Plaque ☐ Guttate ☐ Flexural ☐ Erythrodermic ☐ Pustular ☐ Palmoplantar		Current Lesions ☐ Plaque ☐ Guttate ☐ Flexural ☐ Erythrodermic ☐ Pustular ☐ Palmoplantar		Affected areas ☐ Scalp ☐ Face ☐ Ears ☐ Neck ☐ Arms ☐ Armpits ☐ Dorsum ☐ Palms ☐ Fingernails ☐ Body front ☐ Body Back ☐ Waistline ☐ Genitals ☐ Inguinal ☐ Buttocks ☐ Legs back ☐ Legs front ☐ Feet ☐ Soles ☐ Toenails			
	Personal topicals ☐ Mild soap ☐ Shampoo ☐ Emollients ☐ Virgin coconut oil ☐ Mineral oil ☐ Botanicals ☐ Name brands		Active topicals ☐ None ☐ BL cream ☐ Katialis ☐ Katinko ☐ Tars ☐ Keratolytics ☐ Sulfur		☐ Clobetasol ☐ Betamethasone ☐ Hydrocortisone ☐ Other steroids ☐ Vit. D analogs ☐ Vaseline		Oral Drugs ☐ None ☐ Steroids ☐ Methotrexate ☐ Cyclosporine ☐ Retinoids ☐ NSAIDS		Phototherapy ☐ None ☐ UVB ☐ NB-UVB ☐ UVA ☐ Bath PUVA		Relaxation ☐ None ☐ Prayer/ meditation ☐ Social media ☐ Sports	
PSORIASIS MANAGEMENT	BIOLOGICS ☐ None ☐ Etanercept ☐ Infliximab ☐ Ustekinumab ☐ Secukinumab		Response ☐ Clear/ mostly clear ☐ Same ☐ Worse ☐ Reacted		Administration ☐ Per protocol ☐ On relapse only ☐ On fund availability		Only after? ☐ <1month ☐ 1-2mos ☐ 3-4mos ☐ 5-6mos		☐ 7-8mos ☐ 9-10mos ☐ 11-12mos		Funding ☐ Savings ☐ Loan ☐ Donor ☐ PWD ☐ PCSO ☐ Philhealth ☐ Study ☐ Others	

Page 4

PERCEIVED TRIGGERS / AGGRAVATING FACTORS	Pulmonary ☐ Sore throat ☐ Cough ☐ Colds	Skin ☐ Boils ☐ Acneiform ☐ Pustules	☐ Cellulitis ☐ Ulcers ☐ Herpes	Dental ☐ Cavities ☐ Gum ☐ Impacted ☐ Canker sores	Urinary Tract ☐ Frequency ☐ Incontinence ☐ Flank pain ☐ Dysuria	
	Atopy ☐ Asthma ☐ Rhinitis ☐ Skin Asthma Hepatitis ☐ A ☐ B ☐ C	Arthritis ☐ Psoriatic ☐ Gout ☐ Rheumatoid ☐ Osteoarthritis	Other Dermatoses ☐ Contact ☐ Hives ☐ Rashes ☐ Blisters	Diabetes ☐ Juvenile ☐ Adult ☐ High BP ☐ Heart ☐ Obesity	☐ Thyroid ☐ PTB ☐ Atypical mycobacteria ☐ COPD	☐ Obesity ☐ Fatty liver ☐ Dyslipidemia ☐ UTI ☐ Cystitis ☐ Nephritis
	Medications & Supplements (list ALL below)					
	Personal stress ☐ <7-8h sleep ☐ Cigarettes ☐ Alcohol ☐ Depression ☐ Suicidal thoughts ☐ Family ☐ Relations ☐ Sickness ☐ Death	Usual Food Choices ☐ Red meat ☐ Poultry ☐ Fish ☐ Shellfish ☐ White Rice ☐ Brown/Red Rice	☐ White bread ☐ Wheat bread ☐ Pastries ☐ Fruits ☐ Vegetables ☐ Junk Foods ☐ Fast foods	Cooking oils: ☐ VCO/ Coconut ☐ Palm ☐ Olive ☐ Canola ☐ Soybean ☐ Other seed oils	Allergies ☐ Food ☐ Medicine ☐ At Work ☐ At Home ☐ In school ☐ At Play ☐ Cosmetics ☐ Skin care ☐ Footwear ☐ Clothing ☐ Sports	
PATIENT'S UNMET NEEDS	Mark ✓ if satisfied. Mark ✗ if not satisfied	Dermatologist ☐ Management ☐ Time spent ☐ Explanation	Rheumatologist ☐ Management ☐ Time spent ☐ Explanation	Government Support ☐ Formulary/ Medications ☐ Philhealth (pass Bill-719) ☐ > PCSO support ☐ MD-initiated research funds approval	Distribution ☐ Direct to MDs only ☐ Instruction thorough Packaging secure if given to patient	Pharma Co. ☐ Support for research ☐ ↓ drug costs

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Lesion severity score photos to guide you 0:Clear; 1:Mild; 2:Moderate; 3:Severe; 4:Very Severe					
E : Erythema Redness		I : Induration Thickness		S : Scaling	
	(0)		(0)		(0)
	(1)		(1)		(1)
	(2)		(2)		(2)
	(3)		(3)		(3)
	(4)		(4)		(4)

With an X, Tick Patient's Scores Here as noted on the left			
Area	(E)	(I)	(S)
Head Neck	☐ (0)	☐ (0)	☐ (0)
	☐ (1)	☐ (1)	☐ (1)
	☐ (2)	☐ (2)	☐ (2)
	☐ (3)	☐ (3)	☐ (3)
	☐ (4)	☐ (4)	☐ (4)
Upper Limbs	☐ (0)	☐ (0)	☐ (0)
	☐ (1)	☐ (1)	☐ (1)
	☐ (2)	☐ (2)	☐ (2)
	☐ (3)	☐ (3)	☐ (3)
	☐ (4)	☐ (4)	☐ (4)
Trunk Axilla Groin	☐ (0)	☐ (0)	☐ (0)
	☐ (1)	☐ (1)	☐ (1)
	☐ (2)	☐ (2)	☐ (2)
	☐ (3)	☐ (3)	☐ (3)
	☐ (4)	☐ (4)	☐ (4)
Lower Limbs Butt	☐ (0)	☐ (0)	☐ (0)
	☐ (1)	☐ (1)	☐ (1)
	☐ (2)	☐ (2)	☐ (2)
	☐ (3)	☐ (3)	☐ (3)
	☐ (4)	☐ (4)	☐ (4)

Retrieved from: https://www.pasitraining.com/calculator/step_1.php

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Correlation of CT Epicardial Adipose Tissue (EAT) Thickness with Cardiovascular Risk Using the Framingham Risk Score*

Alex Gian B. Olfato II, MD¹

Abstract

Background. Epicardial adipose tissue (EAT) thickness as a marker of cardiovascular risk has not been extensively studied. Though readily seen in CT images, it is often overlooked due to limited information of its significance. This study aims to determine the correlation of CT EAT thickness with cardiovascular risk using the Framingham Risk Score in adult Filipino patients.

Methodology. This study is a cross-sectional study involving 44 Filipinos, 21 to 70 years, who underwent chest CT scan, CT aortogram, CT calcium score, CT coronary angiogram and CT pulmonary angiogram in our institution from January 2017 to June 2018. After undergoing CT scan, patients are recruited to participate in which their Framingham Risk Score (FRS) was determined. EAT thickness measurements will be measured in the right ventricular anterior free wall along the axial plane. Correlation between EAT thickness and FRS will be analyzed using Pearson's Product – Moment Correlation.

Results. Findings suggest that FRS has a moderate correlation with EAT thickness ($r = 0.6287$, $p = <0.001$).

Conclusion. CT measured EAT shows moderate correlation with Framingham Risk Score.

Key words: Epicardial Adipose Tissue Thickness, Framingham Risk Score.

*2nd Place, 2019 Philippine Medical Association Original Research Presentation Contest, May 15, 2019

¹Resident, Philippine Heart Center, Quezon City

INTRODUCTION

Cardiovascular disease is a global concern and has long become the number one cause of mortality in the Philippines. According to 'The 2013 Philippine Health Statistics' of the Department of Health National Epidemiology Center, 'Disease of the Heart' is the top cause of mortality in both sexes, hence emphasizing how much importance we must put on cardiovascular care (1). Obesity is highly predictive of cardiovascular events and contributes to diastolic dysfunction (2, 3). Fat, which is mainly accumulated in subcutaneous tissue, is also deposited around visceral organs in the abdominal or thoracic regions (3). One of which is the epicardial adipose tissue which is the fat located between the myocardium and visceral layer of the pericardium (3). Adipose tissues, especially visceral adipose tissue, are highly associated with coronary artery disease and cardiovascular events (2). Several studies also show that adipose tissues also produce many adipokines which affects the cardiovascular system (3).

The Framingham Risk Score (FRS) is a gender-specific algorithm used to estimate the 10-year cardiovascular risk of an individual (4). It has been a widely accepted method in determining patients of high risk for heart disease. On the other hand, Epicardial Adipose Tissue (EAT) thickness, as a marker of cardiovascular risk, has not been extensively studied. Though readily seen and measurable in CT images, it is often overlooked due to the limited information of its significance (5). It is a readily derivable information in chest CT scans, however, its utility is still not well studied. CT scan, together with MRI, provide accurate assessment of epicardial adipose tissue thickness and regarded as the gold standard diagnostic methods for evaluating epicardial fat (3).

Few studies have been done to document the value of EAT thickness and their correlation with cardiovascular risk. In a retrospective review of 356 asymptomatic patients done by Nelson et. al., the study concluded that echocardiographically measured EAT thickness is weakly correlated to FRS ($r=0.21$, $P < 0.0001$). In a cross-sectional observational study done by Cetin et. al. involving 127 untreated hypertensive patients, it also reported a positive correlation in EAT thickness and FRS ($r = 0.414$, $p < 0.001$). This study aims to determine the correlation of CT derived Epicardial Adipose Tissue thickness with Framingham Risk Score in adult Filipino patients.

MATERIALS AND METHODS

Institutional Review Board (IRB) approval was obtained prior to the initiation of the study. Informed consent was obtained from all participants of the study. The research is a cross-sectional study done in the CT MRI Division of our institution. Participants were chest CT scan, CT aortogram, CT calcium score, CT coronary angiogram and CT pulmonary angiogram patients from January 2017 to June 2018.

Adult Filipinos aged 21 – 70 years old, either inpatient or outpatient, were included in the study. Exclusion criteria were as follows: (1) substantial motion artifacts in CT scan that render inaccurate measurement of the EAT, (2) previous percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, implanted pacemaker, artificial valves or any other artifact-generating metal objects, (3) cardiac or mediastinal lesions that may render poor delineation of EAT (e.g. myxoma, rhabdomyosarcoma, angiosarcoma), (4) thoracic abdominal aneurysm that may interfere in the visualization of the EAT, and (5) previous myocardial infarction or diagnosed heart disease.

Images of the heart were obtained using either a Philips 256- or 40- slice channel configuration. Subjects were scanned in supine position. Participants were then recruited for the study after scanning. Framingham Risk Score was then obtained. Epicardial adipose tissue thickness was measured by the investigator. Three measurements were obtained at the 25%, 50% and 75% levels of the right ventricular anterior free wall along the axial plane (Figure1). EAT was measured from the visceral epicardium to the outer aspect of the myocardium and perpendicular to the surface of the heart. The mean of these measurements were used for analysis. Randomly selected cases were reassessed by another radiologist and T- test was done to establish interobserver variability.



Figure 1. Anterior RV wall levels where epicardial adipose tissue thickness was measured.

Sample size calculation was done using Epi Info version 7, the minimum sample size requirement is at least 44 based on the correlation between EAT thickness and FRS = 0.414(3) with alpha level = 5% and power = 80%.

Data analysis was performed in stata SE version 13. Quantitative variables were summarized as mean and standard deviation, while qualitative variables were tabulated as frequency and percent. Correlation between epicardial adipose tissue thickness and Framingham's Risk Score was analyzed using Pearson's Product – Moment Correlation and was graphically presented in a scatterplot. The level of significance was set at 5%.

Results

The baseline characteristics of the study population (n = 44) is described in Table 1. The population has slightly more males than females. The mean BMI of the participants is on the overweight range and the mean FRS is 9.23 ± 6.72 which place the population in a higher risk for cardiovascular disease.

Age	47.43 + 13.26
Sex	
Male	29 (65.91)
Female	15 (34.09)
Height (m)	1.60 + 0.10
Weight (kg)	66.98 + 13.98
BMI	25.95 + 3.74
Blood Pressure	
Systolic	128.41 + 19.40
Diastolic	77.73 + 7.74
Mean Arterial Pressure	94.57 + 10.52
Lipid Profile	
Total Cholesterol	190.68 + 49.15
Triglycerides	123.23 + 39.30
HDL	51 + 14.93
LDL	115.95 + 40.98
Framingham Risk Score	9.23 + 6.72
EAT (mm)	3.05 + 2.13
Co-morbidities	
Hypertension	16 (36.36)
Diabetes Mellitus	6 (13.64)
PTB	7 (15.91)
CA	0
CAD	7 (15.91)
Breast CA	2 (4.55)
Papillary Thyroid CA	1 (2.27)
Non-Hodgkins Lymphoma	1 (2.27)
Pulmonary abscess	1 (2.27)
CDK	1 (2.27)
PTB/Lung CA (including mets)	7 (15.91)
Gallstones	1 (2.27)
Hypercholesterolemia	9 (20.45)
AAA	1 (2.27)
Neurofibromatosis	1 (2.27)
Aneurysm	1 (2.27)
Arthritis	1 (2.27)
Colon CA	1 (2.27)
Chronic Limb Ischemia	1 (2.27)
Lung Adenocarcinoma	1 (2.27)
Medication	
ACE Inhibitor	2 (4.55)
ARB	8 (18.18)
Beta Blockers	4 (9.09)
CCB	5 (11.36)
Angiotensin II receptor Blocker + CCB	1 (2.27)
Beta-Blocker + Diuretic	1 (2.27)

There is a moderate direct correlation of CT measured EAT with FRS ($r=0.6287$, $p<0.0001$) as shown in Figure 2.

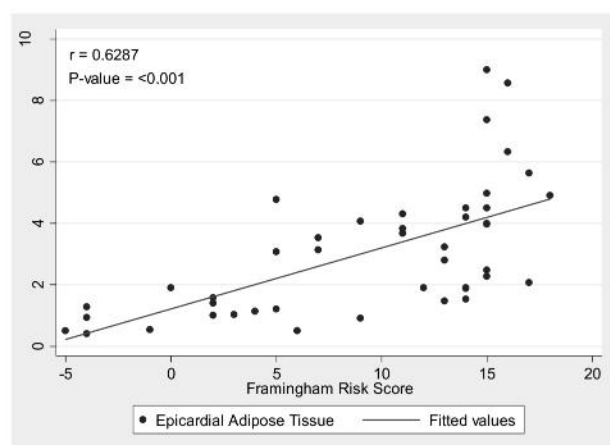


Figure 2. Scatter plot of Epicardial Adipose Tissue versus Framingham

Bland-Altman test was used to demonstrate the interobserver difference done by two radiologist in measuring the epicardial adipose tissue thickness. The test shows good interrater agreement with a p-value of 0.016 (Figure 3).

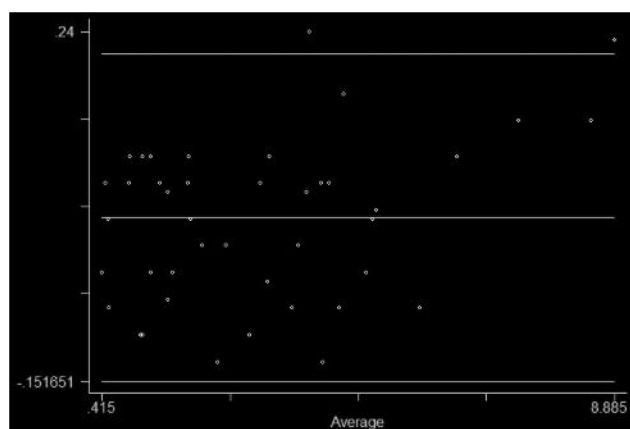


Figure 3. Inter-rater agreement of two Radiologist on Epicardial Adipose

Discussion

This study demonstrates that CT measured EAT thickness is moderately correlated with FRS. Few other studies documented this correlation using 2D- echocardiography derived EAT thickness. In a retrospective review of 356 asymptomatic patients done by Nelson et. al., they reported that 2D echo

measured EAT thickness is weakly correlated to FRS ($r = 0.21$, $P < 0.0001$) (2). In a cross-sectional observational study done by Cetin et. al., involving 127 untreated hypertensive patients, they reported a much higher correlation of EAT thickness, obtained by 2D echo, with FRS ($r = 0.414$, $p < 0.001$) (3).

According to Cetin et. al., EAT thickness is a stronger predictor of coronary artery disease than visceral adipose tissues located in other parts of the body. Embryologically, EAT is similar to abdominal visceral adiposity (3). It is a special fat depot which is related more to visceral fat than total adiposity and shares the same microcirculation with myocardial tissue (3). They also reported that EAT may be a source of several pro-inflammatory and pro-atherogenic cytokines. In addition, they also theorized that EAT may contribute to enhance myocardial hypertrophy, myocardial fibrosis, and perivascular fibrosis. Furthermore, EAT is also associated with diastolic dysfunction, non-dipper status, increased left atrial size and lower ejection fraction, arterial stiffness, higher coronary calcium score, and reduced regional systolic motion (3).

CT scan provides very good anatomic depiction of the epicardial adipose tissue. EAT thickness is readily identifiable and measurable in any CT scans that include the heart. EAT measurements is easy to do and reproducible. This study shows that EAT thickness may provide information regarding a patient's cardiovascular risk.

This study is limited by the time period through which the study was undertaken. Increasing the number of participants may further establish the value of EAT thickness with regards to its correlation in assessing cardiovascular risk. To further determine the significance of EAT thickness, one can correlate it to stratified data providing more specific information.

Conclusion

CT measured EAT thickness is moderately correlated with Framingham Risk Score.

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Appendices

Table 2. Age scoring. Framingham Risk Score for males.

Age, y	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Table 3. Cholesterol scoring. Framingham Risk Score for males

Total Cholesterol mg/dL	Points				
	Age 20-39 y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

Table 4. HDL scoring. Framingham Risk Score for males.

HDL, mg/dL	Points
≥60	-1
50-59	0
40-49	1
<40	2

Table 5. Blood pressure scoring. Framingham Risk Score for males.

Systolic BP, mmHg	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Table 6. Final scoring. Framingham Risk Score for males.

Point Total	10-Year, %
<0	<1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
x17	x30

Table 7. Age scoring. Framingham Risk Score for females.

Age, y	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Table 8. Cholesterol scoring. Framingham Risk Score for females.

Total Cholesterol mg/dL	Points				
	Age 20-39 y	Age 40-49 y	Age 50-59 y	Age 60-69 y	Age 70-79 y
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
x280	13	10	7	4	2

Table 9. HDL scoring. Framingham Risk Score for females.

HDL, mg/dL	Points
x60	-1
50-59	0
40-49	1
<40	2

Table 10. Blood pressure scoring. Framingham Risk Score for Females

Systolic BP, mmHg	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
x160	4	6

Table 11. Final Scoring. Framingham Risk Score for females.

Point Total	10-Year, %
<9	<1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
x25	x30

Knowledge, Attitude and Practice of Filipino Gynecologists on Menopausal Hormonal Therapy: Where Are We Now?*

Mary Grace M. Villafuerte, MD¹

Abstract

Objective: This study will evaluate the knowledge, attitude and practice of gynecologists towards hormonal therapy for menopausal symptoms.

Methods: A descriptive study design was carried out across the different regions of the Philippines from April to October 2018. A self-administered questionnaire was used to identify current knowledge, attitude and practice of gynecologists regarding the use of hormonal replacement therapy.

Results: A total of 369 respondents were able to complete the questionnaire. Our findings indicate that the most common indication for giving MHT are vasomotor symptoms such as hot flushes, night sweats, diaphoresis, vaginal dryness and its associated discomfort and pain during intercourse. Almost all Filipino gynecologists participating in this study are aware that MHT will improve vasomotor, urogenital symptoms, sexual dysfunction and mood. Majority of Filipino gynecologists who participated in this study agreed correctly that MHT will decrease the risk of osteoporosis and coronary artery disease. However, still majority of Filipino gynecologists do not routinely recommend/offer the use of MHT to every postmenopausal woman. On the other hand, at least half of the respondents falsely believe that MHT can decrease the risk for cognitive dysfunction, cerebrovascular disease, Parkinson's disease and vascular thrombosis.

Conclusion: The overall knowledge of Filipino gynecologist who participated in this study is lacking. Only 68% of them agreed that they have adequate knowledge about the treatment options for postmenopausal symptoms and as much as 32% of them are still not confident. Basic knowledge on menopausal symptoms and indications for hormonal therapy are known to the respondents but these knowledge does not translate to practice.

Key Words: hormone replacement therapy, menopause, postmenopause

*3rd Place, 2019 Philippine Medical Association Original Research Presentation Contest, May 15, 2019

¹Resident, Philippine Heart Center, Quezon City

INTRODUCTION

Vasomotor symptoms are the most frequently reported symptoms of women going into menopause. As such, it is the most frequent indication for starting hormonal therapy.^{1,2} Several studies have already recommended menopausal hormone therapy or MHT as an effective way to treat other menopausal symptoms, improve quality of life, alleviate the burden of disease, provide cardiovascular protection and prevent long-term complications (i.e. osteoporosis).³ Controversy and debate regarding the use of MHT started in 2002 when the Women's Health Initiative was published.⁴ Its results suggest an increased risk for cardiovascular disease, Alzheimer's disease, breast cancer, stroke, heart attack, and venous thrombosis. The risk was particularly high for heart attacks in the first year of hormone use and the risk was continued for several years thereafter.^{5,6} As a result, there was a dramatic decrease in the use of hormonal therapy exemplified by the drastic decrease in the sales of hormonal products in the market.^{7,8} Several studies have also observed significant change in the attitude of health professionals towards prescribing hormonal therapy.^{6,9,10,11,12} Among these were the study of Pedersen and colleagues (2007) on Scandinavian gynecologists (Denmark, Sweden and Norway), Moen and colleagues (2005) on Norwegian gynecologists and Meherishi and colleagues (2010) on Indian gynecologists.¹⁴

Despite the tremendous impact of the WHI trial on the practice of gynecologists in the management of menopausal patients, results of the said study remained debatable. In fact, more than fifteen years after its publications, most of its conclusions and recommendations have been reversed as a result of reinvestigation of its own data and conduct of more studies that have proven the efficacy and safety of MHT. As such, updated guidelines for MHT published by various societies including the North American Menopause Society, International Menopause Society and even the Philippine Society of Climacteric Medicine have recommended the use of MHT. Despite these numerous current publications, many health professionals involved in the care of women, particularly gynecologists, have remained cautious in prescribing hormonal therapy for their patients.

A large portion of the world's population is comprised of individuals aged 50 years old and above. Hence, one important aspect of medicine is addressing the medical complications associated with aging, menopause included. It is common knowledge that the attitude and knowledge of gynecologists (or any physician) on hormonal therapy play an important role in the decision making of a woman in her climacteric period. Fifteen years since the publication of the WHI, and in light of the recent recommendations of major organizations on the care of menopausal women, it is worthwhile to explore the current knowledge, attitude and practices of Filipino gynecologists regarding the use of MHT. Specifically, this study aimed to:

1. Identify the indications used by gynecologists in prescribing hormonal therapy (knowledge)
2. Determine the perception of gynecologists on menopausal hormonal therapy (attitude)
3. Determine the prescribing habits of gynecologists (practice)
4. Compare the knowledge, attitude and practices of gynecologists based on their age, years of practice, area of practice, subspecialty and type of practice

With this study, we aim to contribute on how to improve medical service to our aging population and in turn, improve the quality of life of women of menopausal women.

METHODOLOGY

This was descriptive study carried out across the different regions of the Philippines for six months, from April 2018 to October 2018. A questionnaire was used to identify current knowledge, attitude and practices of gynecologists regarding the use of Menopause Hormone Therapy. This study was conducted across the different regions of the Philippines involving gynecologists who were:

- (1) Fellows of the Philippine Obstetrics and Gynecology Society (POGS)
- (2) Aged 30 years old or more
- (3) Currently in the practice of obstetrics and gynecology

Physicians, both general practitioners and practicing gynecologists who were not members of POGS were excluded in the study population. Likewise, POGS fellows who have not been in the practice of OB-GYN for the past 5 years were excluded from the study.

A self-administered questionnaire, adapted from a study done by Nassar and colleagues on menopausal hormonal therapy, was used.¹² The questionnaire was altered to better cater to the population intended to be described by this study. At present, there are no available Philippine data describing the knowledge, attitude and practice of gynecologist practicing in the Philippines. Hence, the investigators chose to use the questions pertaining to the knowledge, attitude and practice after the WHI study.

The modified questionnaire contained questions covering various domains of knowledge, attitude and practices of Filipinos related to MHT. Content validity was assessed by five experts who are members of the Philippine Society for Climacteric Society and were chosen based on their contribution in the field. Each expert was requested to rate each item. The items that had a content validity index (CVI) of 0.8 (or 80% of the experts rated an item as quite or highly relevant) were accepted (see Table 1).

For the face validity, a qualitative assessment was done by ten (10) participants, who are members of POGS. Each item was reviewed, and the subjects were asked the following questions: *Did you have any difficulty understanding this question? What does the question mean to you? Is the question relevant to you?* The questionnaire was modified accordingly (see Table 2).

Lastly, test-retest reliability was assessed by administering the modified questionnaire to ten (10) participants who are members of POGS and re-administering it again within 3-7 days. It was assumed that during this period there will be no expected change in their answers. The investigator then computed for the intraclass correlation coefficient or the kappa between the test and retest results for interval/ratio or nominal variables, respectively. However, items with poor agreement and no agreement were still included because they were deemed necessary to evaluate the knowledge, attitude and practices. The poor/no agreement may be attributed to the lack of knowledge of the participants (see Table 3).

After the validation process, the final questionnaire, containing 22 items with an attached informed consent explaining the objectives of the study and ensuring anonymity of the data, was administered to the participants (Appendix B and C). The self-administered questionnaire had two parts. Part 1 gathered information concerning the patient's demographic data (age, sex), year of residency completion, type of medical practice and subspecialty training. Part 2 was composed of items concerning their knowledge, practice and attitude towards MHT.

Every year, the POGS holds a postgraduate course in the different regions of the country as part of its continuing medical education for members. This became the venue for recruitment of participants for the study and the questionnaires were distributed along with informed consent.

A minimum of 369 subjects was required for this study based on a level of significance of 5%, a prevalence of 40%¹³ with a desired width of confidence interval of 10%, as noted from the reference article by Pedersen et al, 2007.¹⁴

Descriptive statistics was used to summarize the general and clinical characteristics of the participants. Frequency and proportion was used for nominal variables, median and range for ordinal variables, and mean and standard deviation for interval/ratio variables. All valid data were included in the analysis. Missing variables were neither replaced nor estimated. Null hypothesis was rejected at 0.05 α -level of significance. STATA 15.0 was used for data analysis.

RESULTS

A total of 369 respondents were able to complete the questionnaire. Data for analysis were available for almost all of the variables at 97.56 to 100 percent. A stark majority of participants were female (95%), had an age more than 40 years (79%), and were married (73%). Most were practicing both obstetrics and gynecology (99%). More than half obtained an OB-Gyne degree in 2000 to 2018 (57%), were in private practice (55%), had more than ten years of medical experience (72%), and had a subspecialty (60%). The three most common subspecialties were ultrasound (37%), gynecologic oncology (17%) and maternal and fetal medicine (15%). About half of the participants were from the National Capital Region (29%) and Region 6 (21%). Table 4 summarizes the demographic characteristics of the respondents.

Knowledge

Around two for every three respondents (66%) did not routinely recommend MHT for every post-menopausal woman seen in their practice and only offers MHT upon the request of the patient (80%). However, almost all recommended the use of MHT as treatment of vasomotor symptoms such as hot flushes, night sweats, and diaphoresis (95%) and as treatment of vaginal dryness-associated discomfort and pain during intercourse (92%). Still, a majority of respondents recommended the use of MHT for prevention of cardiac accidents such as coronary artery disease (68%), for prevention and treatment of osteoporosis (86%), for treatment of mood changes and emotional lability (84%), and treatment for decrease in libido (80%). About half of the respondents preferred estrogen and progesterone as the first choice of MHT for patients with intact uteri and low risk for cardiovascular events while 73% preferred Tibolone for patients at high risk for cardiovascular events. A vast majority of respondents believed that MHT improves vasomotor symptoms (99%), urogenital symptoms (98%), sexual dysfunction (94%) and mood (93%). About 6-9 in 10 participants also believed that MHT decreases the risk of osteoporosis (93%), cognitive dysfunction (87%), coronary artery disease (77%), cerebrovascular disease (70%), dyslipidemia (65%), Parkinson's disease (65%), and osteoarthritis (62%). However, only 50% believed that MHT decreases the risk of vascular thrombosis while 42% believed that MHT actually increases the risk. On the effect of MHT on breast cancer, there appeared to be no distinct agreement as to whether MHT increases the risk (42%), decreases the risk (30%), or no effect on breast cancer at all (28%). Table 5 summarizes the respondents' knowledge on menopause management.

Attitude

Eight to nine in ten obstetrician-gynecologists agreed that MHT relieved postmenopausal symptoms (97%), improved the quality of life of patients (93%), believed that MHT is an integral part in the care of postmenopausal women (88%), and can prevent chronic disorders such as heart disease, osteoporosis, and cognitive SAD

impairment (87%). On the belief that the respondent had adequate knowledge on treatment options for postmenopausal symptoms, 68% agreed they had adequate knowledge, 2% disagreed, while a third was uncertain. Majority of the respondents will either use MHT or prescribe MHT to his wife/mother/sister (80%) while a diminutive 2% will neither use nor prescribe MHT. Table 6 summarizes the attitudes of respondents towards menopause management.

Practice

Thirty eight percent (38%) of obstetrician-gynecologists had less than six menopausal patients consulting them in the past six months, 37% had six to twelve consults, while a quarter had more than twelve consults. For the past six months, 52% of obstetrician-gynecologists was able to advise MHT to less than 6 menopausal patients, 37% to 6-12 menopausal patients and 12% to more than 12 menopausal patients. During this same period, 60% of obstetrician-gynecologists was able to prescribe MHT to less than 6 menopausal patients, 32% to 6-12 menopausal patients and 8% to more than 12 menopausal patients.

Majority of the respondents screened their patients for menopausal symptoms (76%), discussed symptoms with patients (86%), and offered MHT to women who had bilateral salpingo-oophorectomy (67%). Furthermore, half of the respondents offered MHT only to postmenopausal women within ten years of menopause while a third offered MHT only to those below 60 years old. About 72% would refer patients to another subspecialty for treatment of menopausal symptoms while 28% will not refer their patients. Majority would counsel the patients regarding the possible risks or side effects of MHT but only 33% routinely did the counselling. Similarly, a third reported that they always presented facts about the different forms of MHT to patients and allowed them to participate in decision-making regarding which MHT to choose. Lastly, only 33% would prescribe MHT for a duration of five years and around 29% would also continue the prescription for as long as the drug is tolerated by the patient. Table 7 summarizes the practice of respondents towards menopause management.

DISCUSSION

A larger portion of the world's population is comprised of individuals aged 50 years old and above. As life expectancy rises, more and more women are experiencing the potential long term consequences of menopause. As such, many researches are made to give optimal care for women in pre-menopausal and menopausal years. These studies show that MHT can have significant benefits in women experiencing menopausal symptoms, yet the use of MHT are not common in menopausal patients including Filipino. In a multicenter study done in Latin America shows that only 12.5% of women aged 45-59 use MHT.¹⁵

Our findings indicate that the most common indication for giving MHT are vasomotor symptoms (95%) such as hot flushes, night sweats and diaphoresis, vaginal dryness (92%) and its associated discomfort and pain during intercourse. Menopausal symptoms are observed across nations and experienced by all races, but the prevalence varies across different regions. Hot flushes and night sweats are the most common menopausal symptoms experienced in Caucasian population and similar to the Caucasian population, hot flushes is the most common (56.7%) complain of menopausal Filipino women as shown by the study presented by Gonzaga during the First Consensus Meeting on Menopause in the East Asian Region. However, it was followed by irritability (49.8%), nervousness (47.3%), palpitation (46.8%) and headache (45.9%). Night sweats occur in 44.6% making it only the 6th most common complaint of Filipino menopausal women.¹⁶ Aside from vasomotor and urogenital symptoms, other indications for giving MHT are prevention and treatment of osteoporosis (86%), for mood changes and emotional lability (84%), decrease in libido (80%) and as per patient's request (80%). These findings indicate that vast majority of Filipino gynecologist participating in this study are familiar with the indications and benefits of HRT described in medical literatures and practice guidelines.

Almost all Filipino gynecologists participating in this study were aware that MHT will improve vasomotor (99%) and urogenital (98%) symptoms, sexual dysfunction (94%) and mood (93%). However, despite the overwhelming percentage of Filipino gynecologists believing that MHT relieves menopausal symptoms (97%) and improves quality of life (93%), only 76% of them screen their patients

and only 88% believed that MHT is an integral part in the care of menopausal women. In fact, majority (66%) of Filipino gynecologists do not routinely recommend/offer the use of MHT to every postmenopausal woman.

The knowledge and attitude of gynecologists on hormonal therapy play an important role in the decision making of a woman in her climacteric period. The Philippine Society of Climacteric Medicine, North American Menopause Society and International Menopause Society, among others, have updated clinical practice guidelines for the use of MHT. However, not all gynecologists are knowledgeable on the pre-treatment investigation, the regimen to use and the surveillance needed for MHT. Only 68% of Filipino gynecologists participating in this study agreed that they have adequate knowledge about the treatment options for postmenopausal symptoms (12% strongly agreed and 56% agreed), and as much as 32% of them are still not confident about their knowledge on menopausal treatment. Moreover, although 86% of Filipino gynecologists participating in this study discuss menopausal symptoms with their patients, not all of them advise or prescribe MHT. Majority (75%) of the respondents have 12 or less menopausal patients for the past 6 months (38% with less than 6 and 37% with 6-12 menopausal patients). Of the 25% of Filipino gynecologists who have more than 12 menopausal patients, only 12% was able to advise MHT. And among these 25%, only 8% was able to prescribe MHT to their patients. This indicates that not all menopausal patients were advised on MHT and that not all menopausal patients advised on MHT were given prescription for MHT. In fact, most (72%) of the Filipino gynecologists participating in this study will tend to refer their patients to another subspecialty for the treatment of menopausal symptoms.

Majority of Filipino gynecologists who participated in this study agreed correctly that MHT will decrease the risk of osteoporosis (93%) and coronary artery disease (77%). Based on the 2016 IMS Recommendations, MHT is the most appropriate management for fracture prevention in the early menopause and that MHT (combined therapy regimen) is cardioprotective. However, the use of MHT, solely for primary prevention of coronary heart disease for women more than 60 years old is no longer recommended.¹⁷

On the other hand, at least half of the respondents falsely believe that MHT can decrease the risk for cognitive dysfunction, cerebrovascular disease, Parkinson's disease and vascular thrombosis (87%, 70%, 65% and 50% respectively). Based on the three-arm trial done in women below 60 years old, cognitive function is neither harmed nor improved by MHT.¹⁸ This was similar to the follow-up analyses done 7 years from the termination of the WHI study wherein menopausal patients were exposed to 0.625 mg/day of CEE, with or without continuous MPA. However, some studies would show that there is reduced risk for Alzheimer's disease and dementia when MHT initiated during mid-life.¹⁷ In the same way, MHT is not a treatment option for dementia. Once symptoms are already evident initiation of MHT does not have any benefit on cognitive function nor it does not slow down the disease progression.¹⁷

Similar finding was observed for cerebrovascular and Parkinson's disease. Based on the 13-year follow-up data from the WHI, MHT administration in women less than 60 years old and/or less than 10 years since menopause has no effect on the risk of stroke. This trend was similarly observed with MHT on the risk for Parkinson's disease.¹⁷

Administration of oral estrogen therapy is contraindicated for women with history of venous thromboembolism. Still, half of the respondents believe that MHT decreases the risk for vascular thrombosis. Forty two percent of the respondents were correct that the risk for thromboembolism increases with MHT, especially if given to women more than 60 years old. As such, transdermal estrogen therapy is the first line of treatment for obese women with menopausal symptoms.¹⁷

Data on the risk of breast cancer development for patients on MHT are varied and the use of MHT in women more than 50 years old is a complex issue. In this study, the respondents have varied answer. Thirty percent (30%) believed that MHT decreases the risk of breast cancer, 28% said that MHT has no effect on breast cancer development and the remaining 40% of them believed that MHT increases risk for breast cancer. Studies have shown that there is only small risk of breast cancer attributable to MHT and the said risk would progressively decline after the discontinuation of the medications. The increase risk of breast cancer is primarily associated with synthetic

progesterone added to estrogen (MPA + CEE). However, the risk is lower if micronized progesterone or dydrogesterone will be used.¹⁷

More than half of the respondents (62%) believed that MHT decreased the risk of osteoarthritis. Although there is no clear association between the risk of osteoarthritis and long-term estrogen exposure, studies have shown that cartilage degradation and need for joint replacement surgery are reduced in patients receiving hormonal treatment.¹⁷

Women who underwent bilateral oophorectomy will experience similar symptoms as that of women who had natural menopause. As such, screening, treatment and surveillance for surgically menopause patients should be similar to those who underwent natural menopause. Of the Filipino gynecologists participating in this study, only 67% offer MHT to women who already has surgical menopause. Aside from the above mentioned benefits, estrogen therapy initiated at the time of surgery (oophorectomy) may have short-term cognitive benefit.¹⁷

In a multinational study done in Latin America by Dankers and colleagues (2016), they observed that most gynecologists were supportive of personal use of MHT. This was similar our findings. Eighty percent of Filipino gynecologists participating in this study will use MHT for themselves or for their partners/mother/sister for the male gynecologists. Only 2% disagreed on personal MHT use. A higher percentage of personal use was recorder in Germany (97%) and in US and Europe (92%) but lower in Scandinavia (68% - 74%).^{14,19,20} These difference on the rate of personal use of MHT may suggest that not all physicians accept the reliability of the results of the WHI. This study shows that despite the high percentage of personal use for MHT, this does not translate to clinical practice. Of the 25% of respondents with more than 12 menopausal patients, only a third of them (8% of the total number of respondents) was able to prescribe MHT. In a study done in Latin America, they identified that the main reason for the low rate of MHT use is the lack of medical prescription.¹⁵ And we all know that the use of MHT by menopausal women are strongly influenced by how their physicians counsel them. In the same way, the attitude of gynecologists (or any physician) towards MHT is greatly influenced by their knowledge and the social, cultural and economic settings in which they live.

There were no strict and mandatory rule on the use of MHT but data from recent studies, including the WHI study, suggest that MHT can be safely given up to 5 years in a healthy woman less than 60 years old. The dosage of MHT should be the lowest effective dose so as to minimize the unwanted side effects and maximize its benefits. This study shows that aside from the symptomatology, the primary factors that were considered in giving MHT are age and years of menopause. Half of the respondents will offer MHT only if within 10 years of menopause and 33% of the respondents will only offer MHT to postmenopausal women below 60 years old. A third of the respondents respond in agreement with the recommendation of a 5-year duration of MHT while 29% of them will give MHT as long as the drug is tolerated by the patient. Lastly, patients should be well-informed and is an active participant in the decision making of MHT use.

Factor analysis showed that there is no significant difference in the knowledge and attitude of Filipino gynecologist. Age, years of practice, area of practice, type of practice, and subspecialty, did not affect the knowledge and attitude of Filipino gynecologist. The only significant factors (age and length of practice) was on magnitude of practice, that is, Filipino gynecologists aged more than 50 years and practicing for more than 10 years had greater magnitude of practice (i.e. in terms of number of patients, advice on MHT made, and prescription of MHT in the past six months) as compared to those aged 30-50 years and had 5-10 years of practice. This was similar to the correlation found by Danckers and colleagues (2016) between doctor's age and prescription behavior. The correlation was expected since longer duration of practice will translate to more patients and more experience with using MHT. On the other hand, no significant difference was seen on the magnitude of practice based on areas of practice, subspecialties, and types of medical practice.

CONCLUSION AND RECOMMENDATION

The overall knowledge of Filipino gynecologist who participated in this study was lacking. Only 68% of them agreed that they have adequate knowledge about the treatment options for postmenopausal symptoms (12% strongly agreed and 56% agreed), and as much as 32% of them were still not confident. Only 76% of the respondents screen their patients for menopausal symptoms and 72%

of the respondents will refer their patients to subspecialty clinic to address menopausal complaints. If these menopausal symptoms are not asked during a consult, fewer women will be screened for the long-term consequences of menopause and fewer women will receive the benefits of MHT. Lastly, only a third of the respondents will routinely counsel their patients on risk and side effects of MHT.

Basic knowledge on menopausal symptoms and indications for hormonal therapy are known to the respondents but these knowledge does not translate to practice. As was mentioned, only a third of the 25% of respondents (8% of the total number of respondents) with more than 12 menopausal patients for the past 6 months was able to prescribe MHT. The unfamiliarity with the timing of initiation, type of medication (estrogen only, combined estrogen and progesterone, tibolone, etc.), dosage, manner of administration (oral, dermal, vaginal) and duration of treatment may be the significant factors influencing the low rate of MHT prescription. Further research may explore these factors.

This study recommends that further study be made to explore the level of understanding of Filipino gynecologist on menopause and MHT. A more detailed questionnaire on the different aspects of MHT (timing of initiation, type of medication (estrogen only, combined estrogen and progesterone, tibolone, etc.), dosage, manner of administration (oral, dermal, vaginal) and duration of treatment) may be administered to properly assess the adequacy of knowledge of Filipino gynecologist. In the same way, it may also be necessary to know the knowledge, attitude and practices of physicians in training on MHT. Since administration of MHT is not limited to practicing gynecologists, data on KAP of all physicians can also be gathered. The local data on these data were published last 1996 by Gonzaga and no recent data was found on literature. Administration of this questionnaire to all physicians may differentiate the KAP of gynecologists from other specialist. If future researches will yield the same trend, results can be used to improve the academic and training program of different institution. In effect, results of researches such as this can improve service delivery to menopausal women and be able alleviate symptoms and improve their quality of life.

Table 1. Content validity among experts (n = 5)

Items	Item Relevance Rating				I-CVI	Decision
	Not Relevant	Somewh at Relevant	Quite Relevant	Highly Relevan t		
	Frequency (%)					
Question 1a	0	0	0	5 (100)	1.00	Accepted
Question 1b	0	0	0	5 (100)	1.00	Accepted
Question 1c	0	0	0	5 (100)	1.00	Accepted
Question 1d	0	0	0	5 (100)	1.00	Accepted
Question 1e	0	0	0	5 (100)	1.00	Accepted
Question 1f	0	0	0	5 (100)	1.00	Accepted
Question 1g	0	0	1 (20)	4 (80)	1.00	Accepted
Question 2	0	0	0	5 (100)	1.00	Accepted
Question 3	0	0	0	5 (100)	1.00	Accepted
Question 4a	0	0	0	5 (100)	1.00	Accepted
Question 4b	0	0	0	5 (100)	1.00	Accepted
Question 4c	0	0	0	5 (100)	1.00	Accepted
Question 4d	0	0	0	5 (100)	1.00	Accepted
Question 4e	0	0	0	5 (100)	1.00	Accepted
Question 4f	0	0	0	5 (100)	1.00	Accepted
Question 4g	0	0	0	5 (100)	1.00	Accepted
Question 5a	0	0	0	5 (100)	1.00	Accepted
Question 5b	0	0	0	5 (100)	1.00	Accepted
Question 5c	0	0	0	5 (100)	1.00	Accepted
Question 5d	0	0	0	5 (100)	1.00	Accepted
Question 6	0	0	0	5 (100)	1.00	Accepted
Question 7	0	0	0	5 (100)	1.00	Accepted
Question 8	0	0	0	5 (100)	1.00	Accepted
Question 9	0	0	2 (40)	3 (60)	1.00	Accepted
Question 10	0	0	2 (40)	3 (60)	1.00	Accepted
Question 11	0	0	1 (20)	4 (80)	1.00	Accepted
Question 12	0	0	1 (20)	4 (80)	1.00	Accepted
Question 13	0	0	0	5 (100)	1.00	Accepted
Question 14	0	0	0	5 (100)	1.00	Accepted
Question 15	0	0	1 (20)	4 (80)	1.00	Accepted
Question 16	0	0	0	5 (100)	1.00	Accepted
Question 17	0	0	1 (20)	4 (100)	1.00	Accepted
Question 18	0	0	0	5 (100)	1.00	Accepted
Question 19	0	0	0	5 (100)	1.00	Accepted
Question 20	0	0	0	5 (100)	1.00	Accepted

Table 2. Face validity (n = 10)

	Difficulty in understanding Frequency (%)	Major Comments
Question 1a	1 (10)	1. If given routinely to all postmenopausal women 2. The question is an inquiry concerning my routine MHT practices depending on the symptoms presented by my patient 3. The question is focused on the physician's recommendation to use MHT and yet there is a choice of per request by the patient; an objective indication vs subjective assessment by the patient
Question 1b	1 (10)	1. Two suggested "to include vasomotor symptoms like night swats, hot flushes" 2. The question is an inquiry concerning my routine MHT practices depending on the symptoms presented by my patient
Question 1c	1 (10)	1. Treatment for vaginal dryness 2. The question is an inquiry concerning my routine MHT practices depending on the symptoms presented by my patient 3. It only signifies discomfort. Women oftentimes complain of pain. Maybe a pain scale would be better for further description
Question 1d	1 (10)	1. The question is an inquiry concerning my routine MHT practices depending on the symptoms presented by my patient 2. Need to qualify cardiac accidents
Question 1e	0	The question is an inquiry concerning my routine MHT practices depending on the symptoms presented by my patient
Question 1f	0	The question is an inquiry concerning my routine MHT practices depending on the symptoms presented by my patient
Question 1g	0	I think whether or not the patient requests MHT due to decreased libido, the symptoms should be ask by the doctor
Question 1h	0	No modification required
Question 2	1 (10)	1. It is testing my knowledge on the proper MHT to give / prescribe. It is an inquiry concerning my preference of treatment 2. might need to specify low and high risk

	Difficulty in understanding Frequency (%)	Major Comments
Question 3	1 (10)	Two suggested "to qualify or specify low and high risk"
Question 4a	0	1. Suggest to include specific symptoms for vasomotor symptoms 2. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may have different side effects (or their effects are not all the same?) 3. By experience, the effects of MHT especially on improvement is not ABSOLUTE (as in simply saying improved). Maybe you could sub categorize improvement into a rating scale
Question 4b	1 (10)	1. Suggest to include specific symptoms for urogenital symptoms 2. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may have different side effects (or their effects are not all the same?) 3. Urogenital symptoms are all encompassing terminology. Need to better qualify this statement
Question 4c	1 (10)	1. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may have different side effects (or their effects are not all the same?) 2. Need to qualify mood
Question 4d	1 (10)	1. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may have different side effects (or their effects are not all the same?) 2. Qualify sexual dysfunction
Question 5a	0	This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may have different side effects (or their effects are not all the same?)

	Difficulty in understanding Frequency (%)	Major Comments
Question 5b	0	1. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may hae different side effects (or their effects are not all the same?) 2. I find the question a bit confusing. I suggest to modify a bit e.g. based on your current knowledge, what are the effects of MHT on the following conditions.
Question 5c	0	1. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may hae different side effects (or their effects are not all the same?) 2. I find the question a bit confusing. I suggest to modify a bit e.g. based on your current knowledge, what are the effects of MHT on the following conditions.
Question 5d	0	1. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may hae different side effects (or their effects are not all the same?) 2. I find the question a bit confusing. I suggest to modify a bit e.g. based on your current knowledge, what are the effects of MHT on the following conditions.
Question 5e	0	1. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may hae different side effects (or their effects are not all the same?) 2. I find the question a bit confusing. I suggest to modify a bit e.g. based on your current knowledge, what are the effects of MHT on the following conditions.
Question 5f	0	1. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may hae different side effects (or their effects are not all the same?)

	Difficulty in understanding Frequency (%)	Major Comments
		2. I find the question a bit confusing. I suggest to modify a bit e.g. based on your current knowledge, what are the effects of MHT on the following conditions.
Question 5g	0	1. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may have different side effects (or their effects are not all the same?) 2. I find the question a bit confusing. I suggest to modify a bit e.g. based on your current knowledge, what are the effects of MHT on the following conditions.
Question 5h	0	1. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may have different side effects (or their effects are not all the same?) 2. I find the question a bit confusing. I suggest to modify a bit e.g. based on your current knowledge, what are the effects of MHT on the following conditions.
Question 5i	0	1. This is checking whether I am aware of the different side effects / risks of therapy. / should the exact therapy (i.e. estrogen, tibolone, E-P) be specified as they may have different side effects (or their effects are not all the same?) 2. I find the question a bit confusing. I suggest to modify a bit e.g. based on your current knowledge, what are the effects of MHT on the following conditions.
Question 6	0	The questions are to evaluate my belief concerning practices with MHT towards patients and myself
Question 7	0	The questions are to evaluate my belief concerning practices with MHT towards patients and myself
Question 8	0	The questions are to evaluate my belief concerning practices with MHT towards patients and myself

	Difficulty in understanding Frequency (%)	Major Comments
Question 9	0	The questions are to evaluate my belief concerning practices with MHT towards patients and myself
Question 10	1 (10)	1. The questions are to evaluate my belief concerning practices with MHT towards patients and myself 2. Please qualify WHICH chronic disorder?
Question 11	0	The questions are to evaluate my belief concerning practices with MHT towards patients and myself
Question 12	0	1. These questions ask about the specific practice points and frequency of practicing these / Although the questions are relevant, I would like to suggest that the orders of asking these are arranged in this sequence: 18 - 15 - 16 - 17 - 12 - 13 - 14 2. How many menopausal patients have sought consultation
Question 13	0	1. These questions ask about the specific practice points and frequency of practicing these / Although the questions are relevant, I would like to suggest that the orders of asking these are arranged in this sequence: 18 - 15 - 16 - 17 - 12 - 13 - 14 2. For me, questions 13 and 14 are the same 3. Frequency by which I have advised MHT tho the menopausal patients who have sought consultation
Question 14	0	1. Could it be possible to state the difference of sometimes and often? Like sometimes 30-40% of my patients or often 70-80% of the time 2. These questions ask about the specific practice points and frequency of practicing these / Although the questions are relevant, I would like to suggest that the orders of asking these are arranged in this sequence: 18 - 15 - 16 - 17 - 12 - 13 - 14 3. For me, questions 13 and 14 are the same 4. Frequency by which I have prescribed MHT tho the menopausal patients who have sought consultation
Question 15	1 (10)	1. These questions ask about the specific practice points and frequency of practicing

Difficulty in understanding		Major Comments
Frequency (%)		
Question 16	0	these / Although the questions are relevant, I would like to suggest that the orders of asking these are arranged in this sequence: 18 - 15 - 16 - 17 - 12 - 13 - 14
		2. Does screening means ALL types of screening for ALL menopausal patients? Or should this be centered on the chief complaint they present with to the doctor?
Question 17	1 (10)	1. Could it be possible to state the difference of sometimes and often? Like sometimes 30-40% of my patients or often 70-80% of the time
		2. These questions ask about the specific practice points and frequency of practicing these / Although the questions are relevant, I would like to suggest that the orders of asking these are arranged in this sequence: 18 - 15 - 16 - 17 - 12 - 13 - 14
Question 18	0	3. Frequency by which I discuss three symptoms they sought consultation with
		1. Could it be possible to state the difference of sometimes and often? Like sometimes 30-40% of my patients or often 70-80% of the time
Question 19	0	2. These questions ask about the specific practice points and frequency of practicing these / Although the questions are relevant, I would like to suggest that the orders of asking these are arranged in this sequence: 18 - 15 - 16 - 17 - 12 - 13 - 14
		3. Frequency by which I discuss the benefits of MHT and offer it to those who have undergone the said procedure
Question 18	0	1. These questions ask about the specific practice points and frequency of practicing these / Although the questions are relevant, I would like to suggest that the orders of asking these are arranged in this sequence: 18 - 15 - 16 - 17 - 12 - 13 - 14
		2. For the first option, do you mean all MENOPAUSAL women?
Question 19	0	3. Frequency by which I offer MHT to menopausal women based on age groups
		1. Could it be possible to state the difference of sometimes and often? Like sometimes 30-40% of my patients or often 70-80% of

	Difficulty in understanding Frequency (%)	Major Comments
		the time 2. These questions ask about my practices 3. Frequency by which I refer my patients to other specialist for treatment of menopausal symptoms. Connotes I do not know how to manage menopausal women and/or I simply do not have the time explaining the intricacies of menopausal symptoms
Question 20	0	1. Could it be possible to state the difference of sometimes and often? Like sometimes 30-40% of my patients or often 70-80% of the time 2. These questions ask about my practices 3. Frequency by which I advise patients on risks or side effects of MHT
Question 21	0	1. Could it be possible to state the difference of sometimes and often? Like sometimes 30-40% of my patients or often 70-80% of the time 2. These questions ask about my practices 3. Frequency by which I encourage participation of patients in the best MHT suited for her after explain the different forms of MHT
Question 22	0	1. Could it be possible to state the difference of sometimes and often? Like sometimes 30-40% of my patients or often 70-80% of the time 2. These questions ask about my practices 3. Length of time I prescribe MHT.

Table 3. Reliability analysis of the forward translated questionnaire, test-retest analysis

	Observed Agreement	Expected Agreement	Kappa Coefficient	Interpretation	P-value
Question 1a	90%	74%	0.615	Substantial agreement	0.018
Question 1b	100%	100%	-	Perfect agreement	
Question 1c	100%	82%	1.000	Perfect agreement	<0.001
Question 1d	60%	50%	0.200	Poor agreement	0.245
Question 1e	70%	54%	0.348	Fair agreement	0.123
Question 1f	90%	54%	0.783	Substantial agreement	0.006
Question 1g	100%	50%	1.00	Perfect agreement	<0.001
Question 1h	80%	50%	0.600	Moderate agreement	0.029
Question 2	70%	48%	0.423	Moderate agreement	0.033
Question 3	90%	55%	0.778	Substantial agreement	0.001
Question 4a	90%	90%	0	No agreement	-
Question 4b	90%	90%	0	No agreement	-
Question 4c	80%	81%	-0.053	No agreement	0.637
Question 4d	80%	73%	0.259	Fair agreement	0.125
Question 5a	70%	46%	0.444	Moderate agreement	0.010
Question 5b	90%	90%	0	No agreement	-
Question 5c	100%	68%	1.000	Perfect agreement	0.001
Question 5d	90%	73%	0.630	Substantial agreement	0.003
Question 5e	70%	33%	0.552	Moderate agreement	0.003
Question 5f	30%	38%	-0.129	No agreement	0.735
Question 5g	80%	41%	0.661	Substantial agreement	0.004
Question 5h	70%	50%	0.400	Fair agreement	0.098
Question 5i	80%	48%	0.615	Substantial agreement	0.018
Question 6	70%	42%	0.483	Moderate agreement	0.022
Question 7	70%	58%	0.286	Fair agreement	0.098

Question 8	60%	49%	0.216	Fair agreement	0.110
Question 9	50%	48%	0.039	Poor agreement	0.433
Question 10	60%	38%	0.355	Fair agreement	0.020
Question 11	80%	38%	0.677	Substantial agreement	0.002
Question 12	100%	82%	1.000	Perfect agreement	<0.001
Question 13	90%	90%	0	No agreement	-
Question 14	90%	90%	0	No agreement	-
Question 15	80%	40%	0.667	Substantial agreement	0.001
Question 16	80%	38%	0.677	Substantial agreement	0.002
Question 17	40%	28%	0.167	No agreement	0.178
Question 18	60%	33%	0.403	Fair agreement	0.030
Question 19	70%	60%	0.250	Fair agreement	0.163
Question 20	80%	34%	0.697	Substantial agreement	0.001
Question 21	80%	33%	0.702	Substantial agreement	0.001
Question 22	80%	17%	0.759	Substantial agreement	<0.001

Kappa statistic interpretation according to Landis and Koch: ≤ 0 , none; 0.01 to 0.20, poor; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; Above 0.81, Almost perfect

The formula for kappa coefficient is: $\frac{p_o - p_e}{1 - p_e}$ where:

p_o is the actual observed agreement, and;

p_e is the expected agreement.

Table 4. Demographic Characteristics

Variables	Frequency (%)
Sex	
Male	19 (5.15)
Female	350 (94.85)
Age group	
30-35	20 (5.42)
36-40	58 (15.72)
41-45	78 (21.14)
46-50	65 (17.62)
>50	148 (40.11)
Marital status (n=368)	
Single	78 (21.20)
Married	267 (72.55)
Widowed	15 (4.08)
Separated	8 (2.17)
OB-Gyne Degree Year (n=306)	
1958-1969	3 (0.98)
1970-1979	7 (2.29)
1980-1989	31 (10.13)
1990-1999	90 (29.41)
2000-2009	114 (37.25)
2010-2018	61 (19.93)
Medical Practice	
Private practice only	202 (54.74)
Government practice	83 (22.49)
University or academe	12 (3.25)
Practicing in an institution accredited for OB-Gyne training	72 (19.51)
Medical Experience	
5-10 Years	105 (28.46)
>10 Years	264 (71.54)
Subspecialty	
No	260 (40.46)
Yes	109 (59.54)
Specific subspecialty (n=109)	
Family planning	1 (0.92)
Gynecologic oncology	18 (16.51)
IDS	3 (2.75)
Pediatric gynecology	0
Minimally invasive surgery	10 (9.17)
REI	6 (5.50)
Trophoblastic Diseases	12 (11.01)
Ultrasound	40 (36.70)
Urogynecology	2 (1.83)
Maternal and Fetal Medicine	16 (14.68)
Multiple subspecialty	1 (0.92)
Practicing (n=368)	
Only OB	0
Only Gyne	5 (1.36)
Both OB and Gyne	363 (98.64)
Area of Practice	
Region 1	20 (5.42)
Region 2	9 (2.44)
Region 3	27 (7.32)
Region 4A	57 (15.45)
Region 4B	0
Region 5	2 (0.54)
Region 6	77 (20.87)
Region 7	18 (4.88)
Region 8	5 (1.36)
Region 9	0
Region 10	17 (4.61)
Region 11	17 (4.61)
Region 12	11 (2.98)
Region 13	0
NCR	107 (29.00)
CAR	2 (0.54)
ARMM	0

Table 5. Knowledge towards menopause management

Variables	Frequency (%)
Q1a (Routinely recommends MHT for every postmenopausal women) (n=368)	
No	243 (66.03)
Yes	125 (33.97)
Q1b (Treatment of vasomotor symptoms)	
No	18 (4.88)
Yes	351 (95.12)
Q1c (Treatment of vaginal dryness discomfort and pain during intercourse)	
No	30 (8.13)
Yes	339 (91.87)
Q1d (Prevention of cardiac accidents)	
No	117 (31.71)
Yes	252 (68.29)
Q1e (Prevention and treatment of osteoporosis)	
No	50 (13.55)
Yes	319 (86.45)
Q1f (Treatment of mood changes and emotional lability)	
No	58 (15.72)
Yes	311 (84.28)
Q1g (Treatment for decrease in libido)	
No	74 (20.05)
Yes	295 (79.95)
Q1h (Offers MHT as per request by the patient) (n=368)	
No	75 (20.38)
Yes	293 (79.62)
Q2 (First choice for low risk CVE)	
Estrogen alone	37 (10.03)
Estrogen and progesterone	184 (49.86)
Tibolone	137 (37.13)
Others	11 (2.98)
Q3 (First choice for high risk CVE)	
Estrogen alone	15 (4.08)
Estrogen and progesterone	58 (15.76)
Tibolone	268 (72.83)
Others	27 (7.34)
Q4a (Effect of MHT on vasomotor symptoms) (n=368)	
Worsen	1 (0.27)
No effect	1 (0.27)
Improved	366 (99.46)
Q4b (Effect of MHT on urogenital symptoms)	
Worsen	7 (1.90)
No effect	1 (0.27)
Improved	361 (97.83)

Table 5. Knowledge towards menopause management

Variables	Frequency (%)
Q4c (Effect of MHT on mood)	
Worsen	23 (6.23)
No effect	2 (0.54)
Improved	344 (93.22)
Q4d (Effect of MHT on sexual dysfunction) (n=368)	19 (5.16)
Worsen	2 (0.54)
No effect	347 (94.29)
Improved	
Q5a (Effect of MHT on breast cancer)	
No effect	103 (27.91)
Decreased risk	111 (30.08)
Increased risk	155 (42.01)
Q5b (Effect of MHT on osteoporosis) (n=368)	
No effect	14 (3.80)
Decreased risk	344 (93.48)
Increased risk	10 (2.72)
Q5c (Effect of MHT on cognitive dysfunction)	
No effect	36 (9.76)
Decreased risk	320 (86.72)
Increased risk	13 (3.52)
Q5d (Effect of MHT on coronary artery disease)	19 (5.15)
No effect	285 (77.24)
Decreased risk	65 (17.62)
Increased risk	
Q5e (Effect of MHT on vascular thrombosis) (n=367)	29 (7.90)
No effect	185 (50.41)
Decreased risk	153 (41.69)
Increased risk	
Q5f (Effect of MHT on dyslipidemia)	
No effect	59 (15.99)
Decreased risk	240 (65.04)
Increased risk	70 (18.97)
Q5g (Effect of MHT on cerebrovascular disease)	44 (11.92)
No effect	257 (69.65)
Decreased risk	68 (18.43)
Increased risk	
Q5h (Effect of MHT on Parkinson's disease)	
No effect	114 (30.89)
Decreased risk	240 (65.04)
Increased risk	15 (4.07)
Q5i (Effect of MHT on osteoarthritis)	
No effect	130 (35.23)
Decreased risk	229 (62.06)
Increased risk	10 (2.71)

Table 6. Attitude towards menopause management

Variables	Frequency (%)
Q6 (Belief that respondent had adequate knowledge on treatment options for postmenopausal symptoms)	46 (12.47)
Strongly agree	204 (55.28)
Agree	111 (30.08)
Neutral	7 (1.90)
Disagree	1 (0.27)
Strongly disagree	
Q7 (Belief that MHT improves quality of life of PMW) (n=368)	
Strongly agree	139 (37.77)
Agree	204 (55.43)
Neutral	24 (6.52)
Disagree	1 (0.27)
Strongly disagree	0
Q8 (Belief that MHT is an integral part in the care of PMW)	
Strongly agree	127 (34.42)
Agree	198 (53.66)
Neutral	41 (11.11)
Disagree	3 (0.81)
Strongly disagree	0
Q9 (Belief that MHT relieves postmenopausal symptoms) (n=368)	
Strongly agree	150 (40.76)
Agree	207 (56.25)
Neutral	9 (2.45)
Disagree	2 (0.54)
Strongly disagree	0
Q10 (Belief that MHT can prevent chronic disorder such as heart disease, osteoporosis, and cognitive impairment) (n=367)	
Strongly agree	119 (32.43)
Agree	201 (54.77)
Neutral	40 (10.90)
Disagree	6 (1.63)
Strongly disagree	1 (0.27)
Q11 (For females, will use MHT; For males, will prescribe MHT to his mother/wife/sister)	
Strongly agree	108 (29.27)
Agree	188 (50.95)
Neutral	65 (17.62)
Disagree	8 (2.17)
Strongly disagree	0

Table 7. Practice towards menopause management

Variables	Frequency (%)
Q12 (No. of menopausal patients in ≤ 6 months)	
Less than 6	142 (38.48)
6-12	139 (37.67)
More than 12	88 (23.85)
Q13 (No. of patients advised on MHT in ≤ 6 months)	192 (52.03)
Less than 6	133 (36.04)
6-12	44 (11.92)
More than 12	
Q14 (No. of patients prescribed with MHT in ≤ 6 months) (n=368)	
Less than 6	220 (59.78)
6-12	117 (31.79)
More than 12	31 (8.42)
Q15 (Screens for menopausal symptoms in patients)	7 (1.90)
Never	80 (21.68)
Sometimes	174 (47.15)
Most of the time	108 (29.27)
Always	
Q16 (Discusses menopausal symptoms with patient) (n=367)	
Never	3 (0.82)
Sometimes	48 (13.08)
Most of the time	195 (53.13)
Always	121 (32.97)
Q17 (Offers MHT to women who had bilateral salpingoophorectomy) (n=368)	
Never	7 (1.90)
Sometimes	114 (30.98)
Most of the time	161 (43.75)
Always	86 (23.37)
Q18 (I offer MHT to) (n=360)	
All women regardless of age	40 (11.11)
Only to PMW below 60 years old	120 (33.33)
Only to PMW below 60 years old	17 (4.72)
Only to PMW within her 10 years of menopause	181 (50.28)
Only to PMW within her 20 years of menopause	2 (0.56)
Q19 (Refers patients to another subspecialty for treatment of menopausal symptoms)	
Never	103 (27.91)
Sometimes	208 (56.37)
Most of the time	48 (13.01)
Always	10 (2.71)

Table 7. Practice towards menopause management

Variables	Frequency (%)
Q20 (Routinely counsels patients regarding the possible risks/side effects of MHT) (n=368)	
Never	4 (1.09)
Sometimes	64 (17.39)
Most of the time	180 (48.91)
Always	120 (32.61)
Q21 (Presents fact about the different forms of HRT to patients and allow her to participate in decision-making regarding which HRT to choose)	5 (1.36)
Never	65 (17.62)
Sometimes	186 (50.41)
Most of the time	113 (30.62)
Always	
Q22 (Duration of MHT prescription) (n=368)	
1 year	47 (12.77)
2 years	28 (7.61)
3 years	25 (6.79)
4 years	5 (1.36)
5 years	122 (33.15)
10 years	36 (9.78)
Continue as long as the drug is tolerated by the patient	105 (28.53)

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APPENDIX A

Serial Number: _____

Date: _____

PART I

Instructions: Please place an [x] mark on the appropriate box next to your answer.

Sex	☐ Male	☐ Female
Age	☐ <30 years old ☐ 30-35 years old ☐ 36-40 years old	☐ 41-45 years old ☐ 46-50 years old ☐ >50 years old
Marital Status	☐ Single ☐ Married	☐ Widowed ☐ Separated
OB GYN degree obtained in (year) _____ from _____		
Describe your medical practice:		
	☐ Private practice only	
	☐ Government practice	
	☐ University / Academe	
	☐ Practicing in an institution accredited for OB-Gyn training	
Medical Experience	☐ < 5 years ☐ 5-10 years ☐ > 10 years	
Any subspecialty	☐ Yes	☐ No
If yes,	☐ Family Planning ☐ Gynecologic Oncology ☐ IDS ☐ Pediatric Gynecology ☐ Minimally Invasive Surgery	☐ REI ☐ Trophoblastic Diseases ☐ Ultrasound ☐ Urogynecology ☐ Maternal and Fetal Medicine
Do you practice?	☐ only OB ☐ only Gyne ☐ both OB and Gyne ☐ not practicing for more than 5 years now	
Area of Practice	☐ Region 1 ☐ Region 2 ☐ Region 3 ☐ Region 4A ☐ Region 4B (MIMAROPA) ☐ Region 5 ☐ Region 6 ☐ Region 7 ☐ Region 8	☐ Region 9 ☐ Region 10 ☐ Region 11 ☐ Region 12 ☐ Region 13 ☐ National Capital Region ☐ Cordillera Administrative Region ☐ Autonomous Region in Muslim Mindanao

Please check if you wish to hear the results from us:

☐ I would like to know the result of this study, kindly inform me through my:☐ Email address: _____☐ Postal address: _____

Serial Number: _____

Date: _____

PART II

Instructions: Please place an [x] mark on the appropriate box next to your answer. Select one answer for each question.

A. Your knowledge towards menopause management

1. I recommend the use of Menopause Hormone Therapy (MHT) in the following scenario/s:

a. Routinely to every postmenopausal woman	☐ Yes	☐ No
b. Treatment for vasomotor symptoms (i.e. hot flushes, night sweats, diaphoresis)	☐ Yes	☐ No
c. Treatment of vaginal dryness associated discomfort and pain during intercourse	☐ Yes	☐ No
d. Prevention of cardiac accidents (i.e. coronary artery disease, myocardial infarction)	☐ Yes	☐ No
e. Prevention and treatment of osteoporosis	☐ Yes	☐ No
f. Treatment of mood changes and emotional lability	☐ Yes	☐ No
g. Treatment for decrease in libido	☐ Yes	☐ No
h. As per request of my patient	☐ Yes	☐ No
2. My first choice of MHT for patients with intact uteri and LOW risk for cardiovascular events is

☐ estrogen alone
☐ estrogen and progesterone
☐ Tibolone
☐ others _____
3. My first choice of MHT for patients with intact uteri and HIGH risk for cardiovascular events is

☐ estrogen alone
☐ estrogen and progesterone
☐ Tibolone
☐ others _____

For Question 4,

*Worsen refers to a state of having a more unfavorable condition, that is, from having a (relatively) better state to having a (relatively) poorer condition

*Improved refers to a state of being better, that is, from having a (relatively) poor state to having a (relatively) better condition

4. Determine the effects of MHT on the following conditions:

	Worsen	No Effect	Improved
a. Vasomotor symptoms (i.e. hot flushes, night sweats, diaphoresis)	☐	☐	☐
b. Urogenital symptoms (i.e. vaginal dryness, dyspareunia)	☐	☐	☐
c. Mood (temporary state of mind or feeling)	☐	☐	☐
d. Sexual dysfunction (i.e. decreased in libido, dyspareunia)	☐	☐	☐
5. Based on your current knowledge, what are the effects of MHT on the following conditions:

	Decrease Risk	No effect	Increased Risk
a. Breast Cancer	☐	☐	☐
b. Osteoporosis	☐	☐	☐
c. Cognitive Dysfunction	☐	☐	☐
d. Coronary Artery Disease	☐	☐	☐
e. Vascular Thrombosis	☐	☐	☐
f. Dyslipidemia	☐	☐	☐
g. Cerebrovascular Disease	☐	☐	☐
h. Parkinson's Disease	☐	☐	☐
i. Osteoarthritis	☐	☐	☐

B. Your attitude towards menopause management

		Strongly agree	Agree	Neutral	Disagree	Strongly disagree
6.	I have adequate knowledge about the treatment options for postmenopausal symptoms.	☐	☐	☐	☐	☐
7.	I believe that MHT improves quality of life of postmenopausal women.	☐	☐	☐	☐	☐
8.	Offering MHT is an integral part in the care of postmenopausal women.	☐	☐	☐	☐	☐
9.	I believe that MHT relieves menopausal symptoms.	☐	☐	☐	☐	☐
10.	I believe MHT can prevent chronic disorder (i.e. heart disease, osteoporosis and cognitive impairment).	☐	☐	☐	☐	☐
11.	(For females) I will use MHT. (For males) I will prescribe MHT to my mother/wife/sister.	☐	☐	☐	☐	☐

C. Your practice towards menopause management

12 For the past 6 months, I have ____ menopausal (natural and surgical) patients.

☐ less than 6 ☐ 6-12 ☐ more than 12

13 In the past 6 months, I was able to advise MHT to ____ patients.

☐ less than 6 ☐ 6-12 ☐ more than 12

14 In the past 6 months, I was able to prescribe MHT to ____ patients.

☐ less than 6 ☐ 6-12 ☐ more than 12

15 I screen my patients for menopausal symptoms ☐ Never ☐ Sometimes ☐ Most of the time ☐ Always

16 I discuss menopausal symptoms with my patients ☐ Never ☐ Sometimes ☐ Most of the time ☐ Always

17 I offer MHT to women who underwent bilateral salpingo-oophorectomy? ☐ Never ☐ Sometimes ☐ Most of the time ☐ Always

18 I offer MHT

- ☐ to all women regardless of age
☐ only to postmenopausal women below 60 years old
☐ only to postmenopausal women above 60 years old
☐ only to postmenopausal women within her 10 years of menopause
☐ only to postmenopausal women within her 20 years of menopause

19 I refer my patients to another subspecialty for treatment of menopausal symptoms ☐ Never ☐ Sometimes ☐ Most of the time ☐ Always

20 I routinely counsel my patients regarding the possible risks/side effects of MHT ☐ Never ☐ Sometimes ☐ Most of the time ☐ Always

21 During counseling, I present the facts about the different forms of HRT to the patient and allow her to participate in the decision-making regarding which HRT to choose ☐ Never ☐ Sometimes ☐ Most of the time ☐ Always

22 I prescribe MHT for _____.

- ☐ 1 year ☐ 5 years
☐ 2 years ☐ 10 years
☐ 3 years ☐ continue as long as the drug is tolerated by the patient
☐ 4 years

Factors Associated with Compliance to Guidelines on the Use of Antibiotics and correlated with Clinical Outcomes of Pregnant Women Admitted in the Department of Obstetrics and Gynecology of a Tertiary Hospital from January 1, 2018 to December 31, 2018

Christine Remar L. Concepcion, MD¹

Ricardo M. Manalastas, Jr., MD, FPOGS, FPIDSOG²

Abstract

Background: Antimicrobial therapy is an integral part of an acceptable clinical practice in Obstetrics and Gynecology. However, in order for these antimicrobials to deliver the desired clinical outcome, the practice of judicious antibiotic stewardship should be observed. The objective of the study was 1.) To determine the proportion of pregnant women admitted at the Department of Obstetrics and Gynecology who received antibiotics from January 1, 2018 to December 31, 2018, 2.) To determine the proportion of indications for antibiotic administration, 3.) To determine if indications for antimicrobial usage is in accordance with the clinical case, policy guidelines, culture results and antibiogram report, 4.) To determine the percentage of cases not given antimicrobials that should have been started on antimicrobial therapy, 5.) To compare the association of the clinical outcomes among patients given and not given antimicrobials, 6.) To compare the association of the immediate neonatal outcomes among pregnant patients given and not given antimicrobials.

Methods: A retrospective cohort study was done covering a period of 1 year from January to December 2018. The study included all pregnant patients who were admitted and listed based from the master list of the Department of Obstetrics and Gynecology. Included are all the retrieval charts from the records sections whereas gynecologic and those cases with medical records not retrieved were excluded. A total of 3,495 obstetrics patients admitted from January to December 2018 were retrospectively studied. From this group, the complete medical records of 1,092 obstetrics patients were retrieved and included in this study. Detailed clinical information, antibiotics administered, diagnostic and other relevant investigations, and clinical outcomes were recorded from case sheets. After the data were collected from patients' medical records, datas were manually entered into an electronic spreadsheet file, and the data processing and analysis were then carried out using statistical software Stata 13.

Results: There were 1,092 women included in the current study with more than half of them administered or received antibiotics as part of their regimen (n = 663, 60.71%) compared to those not administered antibiotics (n = 429, 39.29%). The results showed that the prevalence of obstetric patients (undelivered, delivered, ectopic pregnancy and abortion) prescribed and given antibiotics was between 57.75 to 63.62 per cent. There was no association between the comparison groups in terms of age (χ^2 : 3.62, p: 0.31), marital status (χ^2 : 1.29, p: 0.26), body mass index classification (χ^2 : 6.88, p: 0.08), hemoglobin level (χ^2 : 1.74, p: 0.19), and number of prenatal consults (χ^2 : 3.13, p: 0.21). There was a significantly higher proportion of women who delivered abdominally that were administered antibiotics (χ^2 : 32.45, p<0.01) as compared to

¹ Principal Investigator. Fellow-in-Training, Infectious Disease Section, Department of Obstetrics and Gynecology, Philippine General Hospital

² Supervising Investigator. Professor and Consultant, Department of Obstetrics and Gynecology, Section of Infectious Diseases, Philippine General Hospital

women who delivered vaginally (spontaneous or assisted), admitted due to ectopic pregnancy, abortion, and medical management. Cephalosporins are the most widely used antibiotics. Cefazolin (60.48%) followed by Cefuroxime (39.97%) were commonly used for pre-operative prophylaxis and urinary tract infection. Other commonly used antibiotics are Clindamycin (3.62%), Ampicillin (3.47%), Amikacin (2.56%), Ceftriaxone (2.11%) and Doxycycline (1.81%). In 803 of cases (74.15%), reason for administration was not recorded in the chart and stated on working impression and final diagnosis. Majority of the antibiotics were empirically given (99.10%). The irrational use of antibiotics among those administered was observed in 564 cases (52.47%) (95% CI: 49.46-55.47%). Rational use was only observed in 99 cases (19.08%). Among those not given antibiotics, 420 cases (80.92%) with adherence to antibiotic guidelines and 9 cases (52.47%) inappropriately not given antibiotics. It can also be noticed that there was an association between administration (and non-administration) of antibiotics – and having an appropriate indication for such action (χ^2 : 718.97, $p < 0.01$). Maternal and neonatal outcomes showed that there was no noted association between the administration of antibiotics, and selected outcomes. Additional morbidity appeared to be slightly increased among those who were not given antibiotics than otherwise (z : -1.90, p : 0.60).

Conclusion: The study demonstrated that most of the antibiotic administration from January 1 to December 31, 2018

Keywords: Antimicrobial therapy, Antibiotic Stewardship, Resistance, Clinical Guidelines were found to be not compliant to practice guidelines.

INTRODUCTION

Background of the Study

Antimicrobial therapy is an integral part of an acceptable clinical practice in Obstetrics and Gynecology. However, in order for these antimicrobials to deliver the desired clinical outcome, the practice of judicious antibiotic stewardship should be observed. Strict adherence to policy guidelines, evidence-based recommendations, culture studies and the hospital antibiogram should result to appropriate selection, dosing, route and duration of antimicrobial therapy. The decreased inappropriate use of antimicrobials will also limit undesirable outcomes such as emergence of life-threatening resistance, toxicity, prolonged hospital stay and subsequent increased expenditures and human productivity losses. But despite these updated guidelines and recommendations, reports of prevalence and emergence of hard-to-treat resistant bacterial strains remain. Antimicrobial resistance is more prevalent in health-care associated bacterial infections compared with community agents. In a clinical background of poor prevention and control of infections, inappropriate antibiotic use enhances the development and spread of antibiotic genes resulting to or in association of resistant determinants. Despite this fact, the universal threat of antimicrobial resistance is sometimes underestimated. The challenge now in the emergence and prevalence of resistant bacterial strains, especially in resource-limited settings, is the adherence to recommended and updated policies and guidelines. Factors such as the influence of pharmaceutical companies also affects how clinicians prescribe antimicrobials. Another factor is the prospect of litigation which leads to a defensive over-prescription of antibiotics.

There is a need to investigate on the adherence to antibiotic policy guidelines as an evaluation and regulation tool to antimicrobial usage. The desired urgent impact is the optimization of antibiotic therapy in a sustained manner through conscious efforts in observing appropriate selection, dosage, duration and route of antibiotics. Efforts are oriented towards education, activities that encourage and promote consistent

practice of antimicrobial stewardship and constant surveillance of antibiotic administration. Overall, the goal, is to have decreased length of hospital stay, broad-spectrum antimicrobial use, antimicrobial costs, and adverse drug events.

Significance

The aim of the study is to provide information on the practice patterns in antibiotic usage and subsequent clinical and neonatal outcomes in the Department of Obstetrics and Gynecology at a tertiary hospital. The clinical and neonatal outcomes are reflective of the appropriateness and effectiveness of antibiotics as to timing, duration, and type of antibiotic regimen.

Knowing the appropriateness and effectiveness of current practices is essential in the improvement of quality patient care. It would motivate clinicians to analyze and alter practice variations that results to morbidity and mortality associated with non-adherence to antibiotic guidelines, culture results and antibiogram reports.

There are no direct benefits but it would intensify surveillance to adherence in recommended policy guidelines. It could lead to implementation of revised protocols designed to address factors that lead to non-adherence to recommendations.

The goal is to optimize and standardize antibiotic use and subsequently reduce rates of antibiotic resistance, hospital expenses, length of hospital stay, avoid adverse drug reactions and toxicity.

Literature Review

The IDSA Guidelines on Institutional Programs to Enhance Antimicrobial Stewardship emphasized the two core strategies that strengthens antimicrobial stewardship. These are prospective audits with direct intervention and feedback between the prescribing clinician and by an infectious specialist and the formulary restriction and preauthorization. Supplements to these two core strategies are education, evidence-based practice guidelines used with correlation with the microbiology and resistance patterns of the hospital, antimicrobial cycling, antimicrobial order

forms, combination therapy, streamlining or de-escalation based on culture results of patients, dose optimization (on the basis of the patient's individual characteristics, causative organisms, site of infection, pharmacokinetics and pharmacodynamic characteristics of the drug), and the parenteral 5oral conversion. The guidelines also emphasized the importance of clinical discretion on the choice of antibiotic therapy and not rely on practice guideline alone.ⁱ

A study was done by Baysari et al to determine whether the intervention of giving feedback to doctors improves policy adherence. It was concluded that the method did not bring significant change. Issues with policy and the approval process were identified. The study recommended the need for support from senior clinicians, identification of roles and responsibilities in antimicrobial stewardship, and the utilization of technology for antimicrobial approval, monitoring of antibiotic use and compliance. Currently, there is no consensus on which metrics are the most optimal to adequately assess the impact of an antimicrobial stewardship program. Due to the challenges associated with outcomes assessment, most studies to date only focused on measuring the impact of an antimicrobial stewardship program on just one or two metrics, most commonly antimicrobial utilization and costs. The study by Morril et al, provided a detailed assessment of the impact of an antimicrobial stewardship program by measuring and assessing clinical outcomes, antimicrobial utilization, costs, resistance, patient safety, and process metrics. However, this extensive assessment proves to be challenging for some institutions.ⁱⁱⁱ

In a prospective study done by Singh et al on the antimicrobial usage in the department of obstetrics and gynecology in a tertiary hospital, a total of 130 out-patient and in-patients were selected in the three-month study. A total of 76.92% of the antimicrobial therapy given were considered rational and in 23.08 % as irrational. The most common obstetrics condition in which antibiotic was prescribed was eclampsia at 23.8%. The other conditions are full term pregnancy in labor, 23%, puerperal sepsis 14.6%, intrauterine death with previous low transverse cesarean section and diabetes 9.23%, pregnancy-induced hypertension

with oligohydramnios 8.43%, 41 weeks with polyhydramnios 7.69%, eight-month amenorrhea with HbsAg carrier with intra-hepatic cholestasis. Beta-lactams were the most commonly prescribed drugs at 47.46% in the following distribution, Ceftriaxone 88%, Cefuroxime 40%, Piperacillin-Tazobactam 22%. Quinolones are the second most commonly prescribed drugs with Levofloxacin at 52% and Ofloxacin at 20%. Amikacin, an aminoglycoside, is the third most commonly prescribed drug at 58%. Metronidazole, a nitroimidazole, came in fourth at 36%. The study only mentioned on the influence of drug companies as one of the factors that influenced the prescribing pattern of clinicians.^{iv}

In a study by Shah et al, among 453 patients admitted in the Department of Obstetrics and Gynecology in India, 431 cases were given antimicrobials with an overall incidence of 95.14% which is a very high rate. The high incidence of antimicrobial prescription was due to fear on the part of the clinicians on post-operative infection if antimicrobials were not given. Out of the 431 cases, only 340 cases were able to meet inclusion criteria. And out of the 340 cases, only 42 cases were appropriately given antimicrobials and the remaining cases were inappropriately given. The study noted that ciprofloxacin was the most commonly used antimicrobials (60.90%) followed by ampicillin (54.54%) and metronidazole (39.69%). However, this changes among patients who has to undergo procedures. For patients who underwent low segment cesarean section, it was noted that Metronidazole (92.7%) was the preferred antimicrobial; Ciprofloxacin (97.4%) and Metronidazole (94.8%) in cases of hysterectomy; Ampicillin (66.6%) in cases of normal delivery with episiotomy. It was observed that postoperative infection was 7.6% in cases of hysterectomy and 4.4% in low segment cesarean section.^v

In another prospective study by Kolasani et al in a rural tertiary care teaching hospital in the south of India, a total of 162 gynecologic in-patients were enrolled. In a duration of one year, an overall total of 1,647 drugs were prescribed. Antimicrobial agents were the most commonly prescribed drugs (35.76%). Metronidazole (oral 17.66%, parenteral 9.68%) was the most commonly prescribed drug followed by Doxycycline (9.68%).^{vi}

In a point prevalence surveillance study done by Ylmaz et al, in the Ankara Education and Research Hospital in Turkey, it was noted that out of 422 in-patients included in the study, 153 (36.2%) were given antimicrobials. The reason for admission of the 153 cases given antimicrobials are distributed as follows: elective surgery in 82 cases (53.6%), 44 (28.8%) for medical treatment, and 27 (17.6%) for emergency surgical procedures. 64 patients (41.8%) were given antibiotics for treatment and 89 patients (58.2%) were given antibiotics for prophylaxis. Of the 64 patients given antibiotics for treatment, the most frequently used antibiotics were metronidazole (15.5%), third-generation cephalosporins (14.4%) and ampicillin-sulbactam (13.3%). The most frequently used antibiotics for prophylaxis were first-generation cephalosporins (56.9%), ampicillin-sulbactam (11.9%), and ceftriaxone (9.2%). Of the 153 cases given antibiotics, 69 patients (45.7%) were appropriately given antibiotics and 84 patients (54.3%) were inappropriately given. Inappropriate use of antibiotics was more frequent in surgical clinics (62.7%) compared with medical clinics (24.1%). The study noted that the reason for the higher inappropriate use of antibiotics in surgical cases is the lack of infectious disease consultation usually requested in patients admitted in medical clinics. It was also noted that of the 84 cases inappropriately given antibiotics, 75 cases were given treatment or prophylaxis not compatible microbiologically and pharmacologically. And out of the 84 cases not given appropriately, 9 cases were started without an indication.^{vii}

In a multicenter point-prevalence study by Usluer et al on the usage of antimicrobial agents in eighteen tertiary care hospitals, the most frequent reason for hospitalization among 9,471 in-patients was due to medical treatment (42.5%), elective surgery (39.6 %), infectious diseases (17.1 %) and emergency surgical procedures (10.4 %). 2,900 patients were given antimicrobials with the highest frequency among surgical cases (81.6%) and medical (55.2%). Among the 2,900 cases, 48.8 % of antimicrobials were given for treatment and 44.2 % for prophylactic use. Empirical treatment was high at a rate of 78.4%. The infection ratio in the cases appropriately given antimicrobials was 30.7% compared with a 57.9 % in the inappropriately given group. The study observed that majority of the

inappropriately given antimicrobials were due to wrong selection of antimicrobial agents and longer duration than indicated.^{viii}

Factors contributing to the inappropriate drug prescription in different healthcare institutions may vary. Example of such factors are as follows: incentives from pharmaceutical companies, persuasive drug promotion, belief that a new drug is better than an older established drug, fear of litigation hence a prescription for every complain of a patient and empiric utilization of broad-spectrum antibiotics. In a prospective observational by Hecker et al, the reasons for unnecessary therapy were identified in a two-week period in an adult ward. Of the 129 patients, 30% were considered given antimicrobials inappropriately. In this study, the antimicrobials were given on extended duration than recommended, antibiotics were given for non-infectious causes and finally colonizing and contaminating agents were treated. 35% of the antimicrobials used inappropriately were anaerobic agents.^{ix} In an audit done by Aly et al on the adherence to antibiotic policy guidelines, 25% of the irrational antimicrobial use were secondary to inaccurate diagnosis of cases, poor knowledge of policy recommendations, concerns of litigation, fear of complications and sense of self-assurance on the part of the clinician. Organizational obstacles were also noted such as the lack of systems to audit and review antimicrobial usage, inconsistent antibiotic availability, failure to change a familiar ward-popular antibiotic weak triage system, the lack of senior support for junior staff, and the overall delay associated with implementation of policies.^x In another retrospective audit by Ahiabu in Ghana, issues that were contributory to high inappropriate use of antimicrobials were secondary to the fee-for-service approach in which higher prescriptions meant higher revenues for the facility. Second is the limited use of diagnostic tools resulting to uncertainty of diagnosis, hence, antibiotics were liberally prescribed to cover for all possible infections. Third is the increase in number of patients gaining access to formal health-care services including free drugs due to insurance. This development led to uninhibited prescribing practices by clinicians due to less consideration on the costs to the patients.^{xi}

In the choice of empiric antibiotics, specific guidelines, culture and susceptibility studies, and the antibiogram are very important tools in decision-making. Culture and susceptibility studies contributes to the de-escalation of initial broad-spectrum empiric antibiotic by confirming infection and providing the specific causative pathogen/s. The antibiogram on the other hand is utilized as a basis in deciding the selection of antibiotic for empiric treatment since it could give the hospital's rates and patterns of antibiotic resistance to most commonly isolated organisms. It is an essential component then of the of the clinician's decision-making process.

For preoperative surgical prophylaxis both in obstetrics and gynecology, current evidences encourage not only on administration of antibiotic prophylaxis but on the appropriate time as well of administration. However, administration of antibiotics at the appropriate time still proves to be a challenge resulting to postoperative infections. A retrospective cohort study done by Bratzler among 34, 133 women who underwent abdominal and vaginal hysterectomies showed that 55.7% of women were given antibiotic prophylaxis 1 hour prior to incision; 92.6% were consistent with published guidelines and 40.7% were discontinued 24 hours after surgery. The study concluded that there is stillroom for improvement in the practice of antimicrobial prophylaxis administration.^{xi}

In a meta-analysis done by Constantine et al, results showed that antibiotic administration preoperatively resulted to significant reduction in the incidence of postpartum endometritis and wound infection. Further, preoperative administration of antibiotics showed no effect with neonatal infection that needed sepsis work-up.^{xii}

A prospective randomized, double-blind, placebo-controlled trial by Sullivan et al, enrolled 357 patients who underwent cesarean section. The patients were classified as to those given Cefazolin 15-60 mins prior to incision and to the controls who were given Cefazolin at the time of cord clamping. Significant reduction in infectious morbidity, and endometritis were noted to those given antibiotic prophylaxis prior to skin incision. Neonatal sepsis, work-ups and the length of stay were not noted to be increased nor affected as well.^{xiii}

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The principle is to establish adequate concentrations in the serum, tissue and wound before bacterial inoculation on the basis on an antibiotic half-life. (SGOC, Bratzler) The Society of Obstetricians and Gynecologist of Canada Clinical Practice Guideline recommendation on antibiotic prophylaxis in abdominal surgery is the administration of a first generation cephalosporin 15-60 minutes prior to skin incision. Cephalosporins are the surgical antibiotic prophylaxis commonly studied and used.

Broader spectrum antibiotics are avoided to prevent antibiotic resistance development. The first generation Cefazolin has a half-life of 2 hours making it the preferred antibiotic prophylaxis because of the longer protection it can give. It is also a pregnancy category B drug. It exhibits coverage for gram positive organisms. A single dose of 1 gram Cefazolin is effective unless procedure will exceed > 3 hours and if there is presence of blood loss of > 1500 ml. For patients >80 kgs or with a BMI of >35, Cefazolin is increased to 2 grams to avoid giving suboptimal concentration on serum and tissue.^{xvxi}

Overuse of antimicrobials has contributed to the emergence and dissemination of antimicrobial-resistant nosocomial pathogens. Current data regarding patterns of unnecessary antimicrobial use in adult hospitalized patients with a variety of medical and surgical conditions are needed to identify types of misuse that might be amenable to intervention and improve clinical diagnosis, management and finally outcome.

OBJECTIVES

General Objective:

This study aims to review antibiotic practice patterns and the association with clinical outcomes among pregnant women admitted at the Department of Obstetrics and Gynecology in a Tertiary Hospital from January 1, 2018 to December 31, 2018 and evaluate if such patterns are indicated by the clinical case, policy guidelines, culture results and the 2018 antibiogram report.

Specific Objectives:

1. To determine the proportion of pregnant women admitted at the Department of Obstetrics and Gynecology who received antibiotics from January 1, 2018 to December 31, 2018.
2. To determine the proportion of indications for antibiotic administration among women admitted at the Department of Obstetrics and Gynecology who received antibiotics from January 1, 2018 to December 31, 2018.
3. To determine if indications for antimicrobial usage is in accordance with the clinical case, policy guidelines, culture results and antibiogram report.
4. To determine the percentage of cases not given antimicrobials that should have been started on antimicrobial therapy in accordance with the clinical case, policy guidelines, culture results, and antibiogram reports?
5. To compare the association of the clinical outcomes among patients given and not given antimicrobials.
6. To compare the association of the immediate neonatal outcomes among pregnant patients given and not given antimicrobials.

METHODOLOGY

Study Design:

A retrospective cohort study whose duration would span from January to December 2018 and would include all pregnant patients who were admitted and listed based from the master list of the Department of Obstetrics and Gynecology will be used for the initial listing of patients. Clinical

Information and screening results will be recorded from case sheets.

Sampling Plan

The study will include all service (charity) patients admitted at Philippine General Hospital who were pregnant between the said study period, and without the exclusion criteria (i.e. not pregnant during the period of data collection) needed for the study.

Based on the review of the annual reports submitted to the department annually, about 3,495 obstetrics patients were admitted just last year, making the Philippine General Hospital, Department of Obstetrics and Gynecology a big tertiary hospital with diverse infectious and non-infectious cases utilizing antimicrobial agents for varied indications. Thus, it is an excellent study site for evaluating antimicrobial usage pattern. Being a training hospital involved in research and utilization of evidence-based guidelines, it is an institution as well that is familiar with the importance of antimicrobial stewardship programs.

Despite the large number of women for inclusion, there are limited cases for the outcomes and no reliable, regular data about these outcomes – as such all eligible pregnant participants will be included in the study.

Sample Size

As previously mentioned, the study population was estimated to be around 3,495 women based on average census of the OB-Admitting Section in 2018. However, the minimum sample size was computed based on a power of 20%, a level of confidence set at 95%, with a hypothesized proportion of women who had received inappropriate antibiotics at 23.08% based on the study by Singh, et al (2017), and an estimated design effect at 3.0 considering for multi-level stratification based on their management during gravidity. The computed sample size was a need for at least 952 women in the current study - but an additional oversampling of 15% was included to account for incomplete data. An additional oversampling of 15% was included to account for incomplete data – resulting to a minimum sample of at least 1,120 women – 840 who delivered vaginally or abdominally, 140 women who were

managed for ectopic pregnancy; and 140 women who were managed in the institution while still pregnant.

Data Collection and Processing Plan

Initial listing based from the master list of the Department of Obstetrics and Gynecology will be done. A research assistant will collect data. The department of Obstetrics and Gynecology will give authority for access to medical records. Without the exclusion criteria, the study will include all service (charity) patients admitted at the Philippine General Hospital who were pregnant between the said study period. Only clinical information required for answering the research questions will be taken. Identifying data will be removed before usage and analysis. Data gathered will be coded. Data collected will be seen by the researchers and members of the regulatory board only. Clinical information and screening results will be recorded from case sheets. Data collected will be manually entered into an electronic spreadsheet file, and the data processing and analysis will be carried out using Statistical Software Stata 13.

Data Analysis Plan

In order to provide an overview of the study population, descriptive statistics such as mean, standard deviation, median and range will be used for numerical data variables, while frequency or percentage will be used for categorical variables.

A z-test of proportions and a Chi-square test of association, or Fisher's exact test, whichever is applicable, will be used to determine if differences in the proportions of women who were given or not given antibiotics; and those who were appropriately or inappropriately given antibiotic for certain disease conditions.

Proportion per categories of the qualitative variables such as those given antibiotics – and those who were given antimicrobials appropriately or otherwise; delivered vaginally or abdominally – will also be described. Point and interval estimates of these proportions for those who have the outcomes will also be determined.

The level of significance for all sets of analysis was set at a p-value less than 0.05 using two-tailed comparisons. Significance levels will be adjusted for multiple comparisons performed, if necessary.

Inclusion Criteria:

All retrieval charts from the records sections admitted at the department from January 1, 2018 to December 31, 2018

Exclusion Criteria

Non-pregnant
Incomplete charts (without OB sheet, etc)

Operational Terms

Antimicrobial Stewardship - Selection of antimicrobials with the least collateral damage to improve the quality of patient care, Clinical outcomes and stabilize rates of resistance through proper selection of drugs, dosing, duration, frequency and route.

Appropriate Use of antimicrobial therapy - When the selection, dose, route of administration, frequency and duration of antibiotic prescribed is according to the clinical case, policy guidelines, microbiological culture and sensitivity and antibiogram results.

Inappropriate Use of antimicrobial therapy - When the selection, dose, route of administration, frequency and duration antibiotic prescribed is not according to the clinical case, policy guidelines, microbiological culture and sensitivity and antibiogram results.

Antibiogram - refers to a cumulative summary of in vitro antimicrobial susceptibility test results obtained with bacteria and/or fungi recovered from patients with infection over a defined period of time in a given healthcare setting.

Improved - resolution of signs and symptoms leading to discharge from hospital.

Morbidity - presence of complications and worsening of condition.

Mortality - death.

Prolonged Hospital Stay - admission date to time of discharge is more than 5 days.

Adverse Drug Reactions - presence of rashes, jaundice, anemia, decreased white cell count etc as a result of drug administration.

Antibiotic Prophylaxis - prevent infection; intended for elective procedures when the incision will be closed in the operating room.

Anemia - Hemoglobin <11.0 g/dl on the first and 3rd Trimester. Hemoglobin < 10.5 g/dl on 2nd trimester.

Sepsis – clinical syndrome that has physiologic, biologic, and biochemical abnormalities caused by dysregulated inflammatory response to infection. Sepsis and the inflammatory response that ensues can lead to multiple organ dysfunction syndrome and death.

Urinary Tract Infection

Asymptomatic Bacteriuria - It is defined as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts >100,000 cfu/ml. A single catheterized urine specimen with one bacterial species isolated in a quantitative count >100 cfu/ml identifies bacteriuria. Significant pyuria (>10 wbc/hpf) or a positive gram stain of unspun urine (>2 microorganisms/oif) in two consecutive midstream urine samples can be used to screen for asymptomatic bacteriuria in facilities where urine culture and sensitivity is not available.

Acute Uncomplicated Cystitis - It is characterized by urinary frequency, urgency, dysuria and bacteriuria without fever and costovertebral angle tenderness. Gross hematuria may also be present. Diagnosed using urine culture and sensitivity tests of a midstream clean-catch urine specimen. In the absence of urine culture, laboratory criteria for the diagnosis of acute cystitis are as follows: presence of significant pyuria on urinalysis defined as, >8 pus cells/mm³ of uncentrifuged urine, or >5 pus cells/hpf of centrifuged urine, a positive leukocyte esterase and nitrite test on dipstick.

Acute Uncomplicated Pyelonephritis - The presence of classic syndrome of fever (T >38 C), chills, flank pain, costovertebral angle tenderness, nausea and vomiting, with or without signs and symptoms of lower urinary tract infection.

Complicated UTI - It is defined as significant bacteriuria plus clinical signs and symptoms which occur in the setting of functional or anatomic abnormalities of the urinary tract or kidneys, presence of an underlying disease that interferes

with host defense mechanisms, any condition that increases the risk of acquiring persistent infection and/or treatment failure such as obstructive uropathy due to carcinoma, bladder outlet obstruction urethral or ureteric strictures, tumor, calculi etc. The cut-off for significant bacteriuria is 100,000 18 cfu/ml. And in catheterized patients, low-level bacteriuria or counts <100,000 cfu/ml maybe significant.

Community Acquired Pneumonia - Clinical diagnosis includes new lung infiltrate plus clinical evidence that the infiltrate is of infectious in origin, new onset fever, purulent sputum, leukocytosis, decline in oxygenation.

PID - Clinical and diagnostic criteria include the following minimum criteria: cervical motion tenderness, uterine tenderness, and adnexal tenderness.

Additional criteria which supports the diagnosis of pelvic inflammatory disease include, oral temperature higher than 101 fahrenheit/38.3 degrees celsius, abnormal vaginal or cervical discharge, white blood cells on saline (>10 polymorphonuclear leukocytes per high-power field), elevated erythrocyte sedimentation rate (>15 mm/h), elevated C-reactive protein, elevated white blood cell count >10,000 cells/ml, and laboratory evidence of Neisseria gonorrhea or chlamydia trachomatis.

Definitive criteria which confirm the diagnosis of pelvic inflammatory disease includes a histopathologic evidence of endometritis, imaging showing thickened, fluid-filled tubes, with or without pelvic free fluid or tubo-ovarian complex, doppler studies suggesting pelvic infection, intra-abdominal findings consistent with pelvic inflammatory disease on laparoscopy.

Intraamniotic Infection - Any pregnancy at the age of viability with fever 38 C lasting at least one hour, or one episode of fever greater than or equal to 38.3 C with a history of at least one of the following: Ruptured bag of waters, prolonged labor, multiple internal examinations plus at least 2 of the following criteria: Uterine pain, offensive-smelling vaginal discharge, maternal tachycardia (>100/min), fetal tachycardia (>160/min), maternal leukocytosis, uterine fundal tenderness, inflammation of the placenta, membranes or umbilical cord (funisitis) upon histopathologic exam.

Endometritis – refers to the infection of the decidua which may extend to the myometrium and parametria; common cause of postpartum febrile morbidity (oral temperature of $>38^{\circ}\text{C}$ on any of the first 10 days postpartum, exclusive of the first 24 hours).

Surgical Site Infection – infection occurring within 30 days operatively in one of 3 locations: superficial at the incision site; deep at the incision site or in other organs or spaces opened or manipulated during an operation.

Septic Abortion - spontaneous or induced, complicated by infection ranging from focal involvement of the endometrial cavity or its contents or both, with or without the involvement of the uterus and its appendages.

Ethical Considerations

The information that we will collect from this research will be kept confidential as per mandate of the RA 10173, Data Privacy Act of 2012. The two important ethical issues related to chart reviews are informed consent, patient privacy and data confidentiality.

The nature of the study and the questions would cause minimal harm should confidentiality or anonymity be breached. Unless required by law, confidentiality of information will be practiced at all times. Only clinical information will be used for the analysis. Specific information linking to individuals shall not be released. Only information required for answering the research questions will be taken to avoid risk of release of information or possibility of misuse that can expose patients to possible harm or social stigma. Identifying data will be removed before usage and analysis. Data gathered will be coded. Data collected will be seen by the researchers and members of the regulatory board only. Such steps will be instructed to research assistants as well. In case of breach of privacy, it will be reported to the PGH Data Privacy Officer.

Since data collected and stored in medical records were not done with the explicit intention of further use in research, there is no a-priori informed consent for the use of data in chart reviews. Due to the retrospective nature of the study, informed consent is considered as unnecessary since it cannot be carried out, absence of patient interaction, history-taking and physical examination. Confidentiality and anonymity of individuals and their data will be observed. In

accordance with the National Ethical Guidelines of Health and Health Related Research 2017, a waiver of informed consent will be requested from the UPMREB panel because the study presents only with minimal risk which does not adversely affects the rights and welfare of those included in the study. The study has no conflict of interest to declare.

RESULTS AND DISCUSSION

There were 1,092 women included in the current study with more than half of them administered or received antibiotics as part of their regimen ($n = 663$, 60.71%) compared to those not administered antibiotics ($n = 429$, 39.29%) as shown in Table 1. The results showed that the prevalence of obstetric patients (undelivered, delivered, ectopic pregnancy and abortion) prescribed and given antibiotics was between 57.75 to 63.62 per cent. The highest proportions of obstetrics cases administered with antibiotics are the following: age group of 18-30 years ($n=418$, 63%), single ($n=426$, 64.25%), gravida 1-3 ($n=534$, 80.54%), high school level ($n=376$, 56.71%), overweight ($n=232$, 34.99%), length of hospital stay 4-6 days ($n=342$, 51.58%), underwent cesarean delivery ($n=312$, 47.06%), normal hemoglobin levels ($n=624$, 94.12%), with 4-6 prenatal visits ($n=309$, 46.96%) at a local health center ($n=356$, 54.35%). There was no association between the comparison groups in terms of age (χ^2 : 3.62, p : 0.31), marital status (χ^2 : 1.29, p : 0.26), body mass index classification (χ^2 : 6.88, p : 0.08), hemoglobin level (χ^2 : 1.74, p : 0.19), and number of prenatal consults (χ^2 : 3.13, p : 0.21). It can be observed that patients who reached elementary level significantly has a higher proportion of women who were not given antibiotics (χ^2 : 7.10, p : 0.03). There was a slightly higher proportion of women who were not given antibiotics among those who have shorter and longer duration of hospital stay, as compared to those who were admitted within four to six days (χ^2 : 7.43, p : 0.02). There was a significantly higher proportion of women who delivered abdominally that were administered antibiotics (χ^2 : 32.45, $p<0.01$) as compared to women who delivered vaginally (spontaneous or assisted), admitted due to ectopic pregnancy, abortion, and medical management. There was a noted association between administration of antibiotics among those women who were seen at the health center and in the hospital (χ^2 : 10.71, $p<0.01$), but there was no noted difference among those with prenatal consultations from the lying-in clinics.

Table 1. Socio-demographic Characteristics of the Study Population

Variables	Overall	Received Antibiotics	Did not Receive	p-value
Number (%)		663 (60.71%)	429 (39.29%)	
Age in years				
15-17 years	62 (5.68%)	33 (4.98%)	33 (4.98%)	0.31
18-30 years	668 (61.17%)	418 (63.05%)	250 (58.28%)	
30-45 years	355 (32.51%)	207 (31.22%)	148 (34.50%)	
46-50 years	7 (0.64%)	5 (0.75%)	2 (0.47%)	
Marital Status				
Single	716 (65.57%)	426 (64.25%)	290 (67.60%)	0.26
Married	376 (34.43%)	237 (35.75%)	139 (32.40%)	
Gravidity				
G1-3	865 (79.21%)	534 (80.54%)	331 (77.16%)	0.11
G4-6	197 (18.04%)	116 (17.50%)	81 (18.88%)	
G7 and up	30 (2.75%)	13 (1.96%)	17 (3.96%)	
Educational Level				
Elementary	113 (10.35%)	58 (8.75%)	55 (12.82%)	0.03*
High school	627 (57.42%)	376 (56.71%)	251 (58.51%)	
Vocational/College	352 (32.23%)	229 (34.54%)	123 (28.67%)	
BMI Category				
Normal	368 (33.76%)	212 (31.98%)	156 (36.53%)	0.08
Underweight	140 (12.84%)	81 (12.22%)	59 (13.82%)	
Overweight	380 (34.86%)	232 (34.99%)	148 (34.66%)	
Obese	202 (18.53%)	138 (20.81%)	64 (14.99%)	
Duration of Confinement				
1-3 days	402 (36.81%)	232 (34.99%)	170 (39.63%)	0.02*
4-6 days	528 (48.35%)	342 (51.58%)	186 (43.36%)	
7 or more days	162 (14.84%)	89 (13.42%)	73 (17.02%)	
Mode of Delivery				
Spontaneous vaginal	530 (48.53%)	288 (43.44%)	242 (56.41%)	<0.01*
Caesarean section	442 (40.48%)	312 (47.06%)	130 (30.30%)	
Vacuum-assisted	89 (8.15%)	50 (7.54%)	39 (9.09%)	
Others	31 (2.84%)	13 (1.96%)	18 (4.20%)	
Hemoglobin Level				
Normal	1019 (93.32%)	624 (94.12%)	395 (92.07%)	0.19
Anemic	73 (6.68%)	39 (5.88%)	34 (7.93%)	
Number of Prenatal Visits				
1-3 visits	158 (14.56%)	100 (15.20%)	58 (13.58%)	0.21
4-6 visits	533 (49.12%)	309 (46.96%)	224 (52.46%)	
7 or more visits	394 (36.31%)	249 (37.84%)	145 (33.96%)	
Health Care Facility				
Health center	627 (57.95%)	356 (54.35%)	271 (63.47%)	<0.01*
Lying-in clinic	198 (18.30%)	123 (18.78%)	75 (17.56%)	
Hospital	257 (23.75%)	176 (26.87%)	81 (18.97%)	

Table 2 showed that Cephalosporins are the most widely used antibiotics by the Department of Obstetrics and Gynecology. Cefazolin (60.48%) followed by Cefuroxime (39.97%) were commonly used for pre-operative prophylaxis and urinary tract infection (based on pyuria or bacteriuria in urinalysis) respectively. Other commonly used antibiotics are Clindamycin (3.62%), Ampicillin (3.47%), Amikacin (2.56%), Ceftriaxone (2.11%) and Doxycycline (1.81%). Majority of the antibiotics were administered as monotherapy (80.39%) through intravenous route (54.15%) vs oral route (45.85%).

Table 2 also showed that administration of antibiotic were commonly given for pre-operative prophylaxis (69.98%) and asymptomatic urinary tract infection diagnosed through pyuria and bacteriuria in urinalysis collected at the admitting section. Other reasons for antibiotic administration were for suspected intra-amnionic infection (3.02%), abortion (0.75%), endometritis (0.60%), ectopic pregnancy (1.51%). In 803 of cases (74.15%), reason for administration was not recorded in the chart and stated on working impression and final diagnosis. Majority of the antibiotics were empirically given (99.10%).

In an unpublished study by Angelo et al on the practice of antibiotic prophylaxis in the same institution, a total of 855 cases who underwent cesarean were reviewed. Cefazolin 1 to 2 grams IV was the prophylactic antibiotic used in 98.71% of cases but only 26.76% of cases were appropriate timing of administration was done. The same findings were noted in this study wherein majority of the pre-operative prophylaxis were given after cutting of incision. Ideally, pre-operative prophylaxis should be given 15-60 minutes prior to skin incision.

Clindamycin, Amikacin and Ampicillin were commonly used for suspected intra-amnionic infection and few cases of endometritis. Irrational use were commonly due to lack of basis for the suspected intraamniotic infection and continuation of antibiotics for more than 48 hours with oral step-down antibiotics to complete 7 days despite having clinical improvement and not culture-guided. In an unpublished study by Taladtad et al in the same institution as this study, 203 cases of intraamniotic infection from January 31, 2018 were reviewed. Fever which remains to be the cardinal manifestation of IAI was not apparent. Only 75 cases (55.15%) presented with fever. Recent

recommendations no longer included uterine tenderness as a clinical criterion but in this study, it was noted that this was the most common symptom present as basis for the diagnosis of IAI. Thirteen percent were diagnosed with closed cervix and intact membranes. And of the 74 cases (54.41%) with biopsy of the placenta, only 29 cases (39.2%) were noted to have histopathologic findings consistent with chorioamnionitis and funisitis.

Majority of obstetrics cases who delivered either vaginally or abdominally were given home medications of Cefuroxime 500 mgs BID x 7 days for pyuria and bacteriuria in urinalysis collected at the admitting section. Patients were asymptomatic and no gram stain or culture studies were requested and noted in charts. The reason was not stated on records and on working impression and final diagnosis.

There were however, cases of third degree to fourth degree perineal lacerations who were not given the recommended antibiotic regimens for such cases.

All cases of ectopic pregnancy were administered pre-operatively with Ceftriaxone 2 grams as a single dose and given oral Doxycycline 100 mgs BID for two weeks. There are no guidelines for antibiotic prophylaxis for ectopic pregnancy but not all cases are due to PID.

Table 2. Distribution of Administration of Antibiotics Across Disease Conditions

Variables	Frequency	Percentage
Type of Antibiotics		
Amikacin	17	2.56
Ampicillin	23	3.47
Ampicillin-sulbactam	5	0.75
Amoxicillin	7	1.06
Azithromycin	3	0.45
Doxycycline	12	1.81
Cefuroxime	265	39.97
Cefazolin	401	60.48
Ceftriaxone	14	2.11
Cefoxitin	9	1.36
Clindamycin	24	3.62
Co-amoxiclav	2	0.30
Erythromycin	8	1.21
Gentamycin	10	1.51
Levofloxacin	2	0.30
Metronidazole	7	1.06
Penicillin G	4	0.60

Variables	Frequency	Percentage
Number of Agents		
Single	533	80.39
Multiple	130	19.61
Two-agents	110	16.59
Three-agents	20	3.02
Route of Antibiotics		
Oral route	304	45.85
Intravenous only	359	54.15
Reason Provided		
Yes	280	25.85
No	803	74.15
Indications		
Prophylaxis	464	69.98
Urinary tract infection	253	38.16
Intra-amniotic infection	20	3.02
Endometritis	4	0.60
Abortion	5	0.75
Ectopic pregnancy	10	1.51
Empirical	657	99.10
Targeted	6	0.90

Table 3 showed that the irrational use of antibiotics among those administered was observed in 564 cases (52.47%) (95% CI: 49.46-55.47%) – which is higher than the estimate by Singh, et al (2017). Rational use was only observed in 99 cases (19.08%). Among those not given antibiotics, 420 cases (80.92%) with adherence to antibiotic guidelines and 9 cases (52.47%) inappropriately not given antibiotics. It can also be noticed that there was an association between administration (and non-administration) of antibiotics – and having an appropriate indication for such action (χ^2 : 718.97, $p < 0.01$).

Table 3. Distribution of Rationality of Antibiotic Use

Given Antibiotics	Overall	Rational	Irrational
Yes	663 (60.71%)	99 (19.08%)	564 (98.43%)
No	429 (39.29%)	420 (80.92%)	9 (1.57%)
Total		519 (47.53%)	573 (52.47%)

Table 4 showed that there were 2 cases (0.30%) of adverse drug reaction among those administered with antibiotics. It can be noted that additional morbidity appeared to be slightly increased among those who were not given antibiotics than otherwise (z : -1.90, p : 0.60) (Table 4). The highest proportions among neonates whose mothers were administered with antibiotics are the following: Birthweight of 2501-3000 grams ($n=259$, 40.475%), term ($n=471$, 73.71%), appropriate for

gestational age pediatric aging ($n=589$, 92.18%), good 1st minute APGAR ($n=593$, 93.09%), good 5th minute APGAR ($n=626$, 98.27%), direct room-in ($n=496$, 77.99%), neonatal pneumonia ($n=50$, 7.86%). The summary of the maternal and neonatal outcomes (Table 4) showed that there was no noted association between the administration of antibiotics, and selected outcomes. These outcomes specifically are: birth weight (χ^2 : 1.47, p : 0.83), gestational age (χ^2 : 0.64, p : 0.73), pediatric aging category (χ^2 : 2.03, p : 0.36), 1st minute Apgar score (χ^2 : 1.19, p : 0.28), 5th minute Apgar score (χ^2 : 0.38, p : 0.54), neonatal disposition (χ^2 : 1.21, p : 0.55), neonatal sepsis (z : -0.43, p : 0.67), pneumonia (z : 0.99, p : 0.32); and mortality (χ^2 : 1.49, p : 0.22).

Table 4. Distribution of Clinical Outcomes across Administration of Antibiotics

	Received Antibiotics	Did not Receive	p-value
Maternal Outcomes			
Adverse drug reaction	2 (0.30%)	-	-
Additional morbidity	1 (0.16%)	4 (1%)	0.06
Birth weight			
1500-2000 g	54 (8.44%)	36 (8.93%)	
2001-2500 g	86 (13.44%)	63 (15.63%)	
2501-3000 g	259 (40.47%)	156 (38.71%)	0.83
3001-3500 g	182 (28.44%)	108 (26.80%)	
>3500 g	59 (9.22%)	40 (9.93%)	
Birthweight Category			
Normal	500 (78.13%)	304 (75.43%)	0.31
Low birthweight	140 (21.88%)	99 (24.57%)	
Age of Gestation			
Term	471 (73.71%)	296 (73.45%)	
Pre-term	110 (17.21%)	65 (16.13%)	0.73
Post-term	58 (9.08%)	42 (10.42%)	
Pediatric Aging Category			
SGA	32 (5.01%)	16 (3.97%)	
AGA	589 (92.18%)	370 (91.81%)	0.36
LGA	18 (2.82%)	17 (4.22%)	
1st minute Apgar			
Good	593 (93.09%)	381 (94.78%)	0.28
Poor	44 (6.91%)	21 (5.22%)	
5th minute Apgar			
Good	626 (98.27%)	397 (98.76%)	0.54
Poor	11 (1.73%)	5 (1.24%)	
Neonatal Disposition			
Direct Rooming-in	496 (77.99%)	317 (78.86%)	
High Risk - DRI	33 (5.19%)	15 (3.73%)	0.55
Neonatal ICU	107 (16.82%)	70 (17.41%)	
Neonatal Outcomes			
Sepsis	43 (6.76%)	30 (7.46%)	0.67
Pneumonia	50 (7.86%)	25 (6.22%)	0.32
Mortality	8 (1.26%)	2 (0.50%)	0.22

Table 5 showed that the highest proportions among neonates whose mothers were irrationally administered with antibiotics are the following: Normal birthweight (n=428, 77.40%), term (n=404, 73.19%), appropriate for gestational age pediatric aging (n=507, 92.85%), good 1st minute APGAR (n=514, 93.45%), good 5th minute APGAR (n=541, 98.36%), direct room-in (n=422, 76.87%), neonatal pneumonia (n=40, 6.98%).

Table 5. Distribution of Clinical Outcomes across Administration of Antibiotics

	Irrational	Rational	p-value
Maternal Outcomes			
Adverse drug reaction	2 (0.35%)	-	0.18
Additional morbidity	4 (0.70%)	1 (0.36%)	0.76
Birthweight Category			
Normal	428 (77.40%)	376 (76.73%)	0.80
Low birthweight	125 (22.60%)	114 (23.27%)	
Age of Gestation			
Term	404 (73.19%)	363 (74.08%)	
Pre-term	97 (17.57%)	78 (15.92%)	0.74
Post-term	51 (9.24%)	49 (10%)	
Pediatric Aging Category			
SGA	30 (3.67%)	18 (3.67%)	
AGA	507 (91.85%)	452 (92.24%)	0.20
LGA	15 (2.72%)	20 (4.08%)	
1st minute Apgar			
Good	514 (93.45%)	460 (94.07%)	0.68
Poor	36 (6.55%)	29 (5.93%)	
5th minute Apgar			
Good	541 (98.36%)	482 (98.57%)	0.79
Poor	9 (1.64%)	7 (1.43%)	
Neonatal Disposition			
Direct Rooming-in	422 (76.87%)	391 (79.96%)	
High Risk - DRI	30 (5.46%)	18 (3.68%)	0.31
Neonatal ICU	97 (17.67%)	80 (16.36%)	
Neonatal Outcomes			
Sepsis	37 (6.46%)	36 (6.94%)	0.75
Pneumonia	40 (6.98%)	35 (6.74%)	0.87
Mortality	7 (1.22%)	3 (0.58%)	0.26

CONCLUSION

More than half of obstetrics patients admitted from January 1, 2018 to December 31, 2018 were administered with antibiotics. Most of the obstetrics patients administered with antibiotics were 18-30 years old, single, gravida 1-3, high school educational attainment, overweight, stayed at the hospital for 4-6 days, underwent cesarean delivery, with normal hemoglobin levels, had 4-6 prenatal consultations at a local health center.

There was no association between the comparison groups in terms of age, marital status, body mass index, hemoglobin levels, and number of prenatal consultations. Significantly, a high proportion of obstetrics patients who reached only elementary level were not given antibiotics. It was also observed significantly that antibiotic administration has a higher proportion among those admitted and underwent cesarean section as compared to being admitted for vaginal delivery, ectopic pregnancy, abortion and medical management. And significant association was also noted between administration of antibiotics among women who were seen at the health center and in the hospital. There was no noted difference among those with prenatal consultations from the lying-in clinics. Cephalosporins, specifically, Cefazolin and Cefuroxime, were the antibiotics commonly used in the Department of Obstetrics and Gynecology for pre-operative prophylaxis and urinary tract infection respectively. Majority of antibiotics administered were empirically given through the IV route and as monotherapy. Reasons and indications for administration were commonly not in records. The study concluded that majority of antibiotic usage was irrational. Maternal and neonatal outcomes showed that there was no noted association between the administration of antibiotics and the selected outcomes.

LIMITATIONS

Because the study is a retrospective design, it will be limited by the information gathered only on the patient's records. These records may not be recorded reliably, incomplete with patient's data, diagnostics and radiologic results. Reasons for administration and failure to receive antimicrobial therapy may not be stated and postoperative complications such as surgical site infections, postpartum endometritis, etc. that occurred days after discharge may not be included.

RECOMMENDATIONS

We highly recommend that the same study be done prospectively either on a combined or separate obstetrics and gynecologic admissions, and to include all patients classified as morbidity and mortality. A separate prospective study among those given antibiotic prophylaxis with out-patient follow-up is highly recommended. A prospective study on all ectopic pregnancy and prevalence of

gonococcal infection is also recommended. The judicious follow-up on the gram stain and culture results should be observed. Updated antibiotic guidelines should be placed on the different sections of the Department of Obstetrics and Gynecology (admitting section, labor room, delivery room, operating room, out-patient and at the wards). An updated manual for guidelines on antibiotic usage and case protocols in the setting of the institution should also be done. Continuation of antibiotic audit weekly by the infectious team should also be constant.

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A Post Marketing Surveillance Study on the Efficacy and Safety of Bosentan for Treatment of Pulmonary Arterial Hypertension among Adult Filipino Patients

Maria Paz B. Mateo, MD, FPCP, FPCCP¹

Teresita S. De Guia, MD, FPCP, FPCCP¹

Kristine Joy L. Tomanan, RN²

Eileen Lara R. Ladines, RN³

Erwin G. Benedicto, MD, MPH³

Carl Abelardo T. Antonio, MD, MPH, FRPSH, MIHM, AFCHSM^{4,5}

Abstract

Background: Pulmonary arterial hypertension (PAH) is a chronic, debilitating disease affecting millions of adults worldwide. With improved knowledge on PAH and better management, long-term survival in patients has significantly increased in the past 20 years. Bosentan is a nonselective, dual endothelin receptor antagonist used in the treatment of PAH. While the drug has already been established to improve exercise capacity and patient survival globally, no study has investigated its clinical effectiveness and safety among Filipino patients yet. A post marketing study was conducted to determine the efficacy and safety of bosentan (125 mg administered twice daily) among adult Filipino patients with PAH.

Methods: A non-randomized, non-comparative, open-label trial was conducted involving adult patients at a tertiary government hospital in Metro Manila. Study duration was from March to September 2012. Primary end points of the study were patients' response to efficacy and safety.

Results: A total of 14 patients were enrolled in the study and 13 included in the analysis. Mean age of the participants was 34 ± 11.54 years. Remarkable changes were observed for 6WMD and small improvements noted for Borg dyspnea index and CPET. There was no difference between baseline and 12th week WHO functional classification. FEV1/FVC, MVV, RV/TLC and sRaw showed modest improvement; there was a notable difference in the systolic PAP vs baseline; PVR, PVRI, SVR and SVRI demonstrated the largest changes via cardiac catheterization and iloprost. Four patients experienced at least one serious adverse event, with one reported as suspected unexpected serious adverse reaction. Out of 13 patients, 10 (76.9%) considered bosentan as effective while 11 (84.6%) considered it safe.

Conclusion: Bosentan improved exercise capacity, pulmonary function and cardiopulmonary hemodynamics among study participants. The drug is generally well-tolerated and effective. Bosentan is among the useful options for treatment of adult Filipino patients with PAH.

Keywords: pulmonary arterial hypertension, bosentan, efficacy, safety

¹ Philippine Heart Center, Quezon City, Philippines

² Department of Community Development, College of Social Work and Community Development, University of the Philippines Diliman, Quezon City, Philippines

³ Johnson & Johnson (Philippines), Inc., Parañaque City, Philippines

⁴ Department of Health Policy and Administration, College of Public Health, University of the Philippines Manila, Manila, Philippines

⁵ Department of Applied Social Sciences, The Hong Kong Polytechnic University, Hong Kong

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic, debilitating disease affecting millions of adults worldwide, higher in frequency with females but more fatal with males. PAH is a syndrome with diverse etiology and pathogenesis, but common to all types is the progressive increase in pulmonary vascular resistance (PVR), which may lead to right ventricular failure and mortality.¹

Due to improved knowledge on PAH and better management, long term survival in patients has significantly improved in the past 20 years. In the 1980s, median patient survival was 2.8 years, compared to six years at present.² Various treatment strategies are currently available for PAH and are divided into three major categories: (1) general measures, (2) supportive therapies and (3) PAH-specific therapies.³ Major predictors of PAH mortality are exercise capacity, WHO functional class and cardiopulmonary hemodynamics.⁴

Central to the pathogenesis of pulmonary arterial hypertension is pulmonary vascular endothelial cell dysfunction.⁵ Bosentan, a PAH-specific therapy, is the first endothelin receptor antagonist (ERA) successfully used in the treatment of PAH⁵, approved for use in North America and Europe in the early 2000s.¹ It is a nonselective, orally active, dual ERA which targets endothelin, a potent endogenous vasoconstrictor and smooth muscle mitogen that is overexpressed in the lungs and plasma of patients with PAH.³

A double-blind, randomized placebo-controlled trial (BREATHE-1) conducted in 27 centers in Europe, North America, Israel and Australia showed that bosentan 125 mg administered twice daily improved patients' six-minute walking distance (6MWD), Borg dyspnea index, WHO functional class and time to clinical worsening.⁶ In another clinical trial (EARLY study), the drug demonstrated improvement of pulmonary vascular resistance and 6MWD in patients with mild symptoms (WHO functional class II).⁷ Long-term studies have also demonstrated the effectiveness of bosentan in terms of improved overall survival,^{4,8} 6MWD,^{9,10} reduction of mean pulmonary arterial pressure,⁹ slower clinical worsening⁹ and

maintenance/improvement of WHO functional class.¹⁰

While the drug has been globally established to improve exercise capacity and patient survival, most of these studies are from Western countries. Studies from East Asia¹¹⁻¹⁴ (China, Taiwan, South Korea, Japan) are available but no study has investigated its clinical effectiveness and safety among Filipino patients yet. A post marketing study was conducted to determine the efficacy and safety of bosentan among adult Filipino patients with pulmonary arterial hypertension (PAH).

METHODS

The study was a non-randomized, non-comparative, open-label trial (Study No. DC.R.008.11) involving Filipino adult patients. Study duration was from 5 March 2012 to 25 September 2012, conducted at a tertiary government hospital in Metro Manila. Patients were assessed at 4th, 8th and 12 weeks of therapy. The primary end point of the study was the patients' response to efficacy and safety.

The participants' clinical and demographic characteristics were collected at baseline. Exercise capacity, arterial blood gas (ABG) levels, pulmonary function tests (i.e. spirometry, diffusion, lung volume/body plethysmography), hemodynamic monitoring parameters (i.e. systolic pulmonary arterial pressure by tricuspid jet, right atrial pressure, right ventricular size, left ventricular size, Doppler right ventricular index, color Doppler tricuspid area, left ventricular systolic function, left ventricular diastolic function, pulmonary artery size), cardiopulmonary hemodynamic parameters (via cardiac catheterization and vasoreactive testing using iloprost) and laboratory parameters (i.e. body mass index [BMI], pregnancy test, alkaline phosphatase levels, liver function test, bilirubin levels, complete blood count [with white blood cell differential count], bleeding/coagulation tests, serum uric acid, blood troponin and brain natriuretic peptide) were assessed during baseline, follow-ups and week 12. Owing to the large number of assessment/diagnostics performed, only the parameters deemed as essential are presented in this paper.

Quantitative data were summarized as mean $\pm$ standard deviation (SD), frequency (number) and percentage (%) distribution. Due to the small sample size, non-parametric tests were used to determine if there were significant changes from the baseline parameters. Wilcoxon matched pairs signed ranks test was used for ordinal data while McNemar test was utilized for dichotomous data.

RESULTS

Baseline Patient Characteristics

A total of 14 patients were enrolled in the study, with 13 as the final number of patients included in the analysis. One patient died before the drug was given and thereafter excluded from the study. Table 1 describes the clinical and demographic characteristics of participants.

The mean age of the patients was 34 ± 11.54 years. There were 12 females and only one male. The primary etiology of eight patients was congenital heart disease (CHD): four with atrial septal defect (ASD), two with ventricular septal defect (VSD), one with patent ductus arteriosus (PDA) and one with patent foramen ovale (PFO).

On the other hand, four had primary or idiopathic PAH and one had PAH associated with systemic lupus erythematosus (SLE).

Other Medications Taken Together with Study Drug

Thirteen (13) other medications were identified as used by participants simultaneously with bosentan during the study period. In descending order of frequency, these are: furosemide (8 or 61.5%), digoxin (7 or 53.8%), spironolactone (6 or 46.2%), sildenafil (3 or 23.1%), allopurinol (1 or 7.7%), aspirin (1 or 7.7%), clopidogrel (1 or 7.7%), diltiazem (1 or 7.7%), kalium durule (1 or 7.7%), levothyroxine (1 or 7.7%), losartan (1 or 7.7%), prednisone (1 or 7.7%) and trimetazidine (1 or 7.7%).

Exercise Capacity, Body Mass Index (BMI) and WHO Functional Classification

As shown in Table 2, there was a mean increase in the patients' distance walked in 6 minutes (6MWD) (24.50 ± 69.66 meters) from baseline to week 12. There was no difference

between the occurrence of dyspnea before and after performing the 6-minute walk test. There was a decrease in the Borg dyspnea index (0.50 ± 1.24) by week 12. To obtain more accurate evaluation of the exercise capacity of study participants, cardiopulmonary exercise testing (CPET) was done. A small improvement (0.73 ± 3.53) in CPET was noted by week 12. As for BMI and WHO functional classification of the patients, no changes were observed compared to baseline data.

Arterial Blood Gas (ABG)

Parameters under ABG (pH, PCO₂, PO₂, BHCO₃, actual base excess [ABE] and oxygen [O₂] saturation) showed some changes from baseline to week 12 (Table 2). Compared to other parameters, PCO₂ (1.21 ± 4.17) and PO₂ (1.28 ± 13.10) demonstrated notable differences in values.

Pulmonary Function Tests (PFTs)

As shown in Table 3, there were modest changes in spirometry and lung volume parameters. Among the remarkable differences were forced vital capacity/forced expiratory volume in 1 second (FEV₁/FVC) (1.09 ± 4.78), maximum voluntary ventilation (MVV) (1.36 ± 9.18), residual volume/total lung capacity (RV/TLC) (2.82 ± 5.19) and specific airway resistance (sRaw) (3.03 ± 4.24).

Hemodynamic Monitoring and Cardiopulmonary Hemodynamic Parameters

There was a notable decrease in the systolic pulmonary arterial pressure (PAP) by tricuspid jet (10.75 ± 30.84) from baseline. Right atrial pressure (1.00 ± 3.59) and left ventricular systolic function (2.50 ± 4.80) had small changes. As for the rest of the hemodynamic parameters (i.e. right ventricular size, left ventricular size, doppler right ventricular index, color doppler tricuspid area, left ventricular diastolic function, pulmonary artery size), differences observed were minimal.

For cardiopulmonary hemodynamic parameters via cardiac catheterization, noteworthy changes in pulmonary vascular resistance (PVR) (182.20 ± 386.72), pulmonary vascular resistance index (PVRI) (175.68 ± 465.49), systemic vascular resistance (SVR) (938.84 ± 1523.01) and systemic

vascular resistance index (SVRI) (1244.23 ± 2642.15) during invasive cardiac catheterization were demonstrated.

On the other hand, results under mean right atrial pressure (mRAP), mean left atrial pressure (mLAP), mean pulmonary arterial pressure (mPAP), mean systemic arterial pressure (mSAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), cardiac index (CI), mixed venous oxygen saturation (SVO₂%) and left ventricular end-diastolic pressure (LVEDP) showed minimal differences from baseline and week 12.

As for cardiopulmonary hemodynamic parameters through vasoreactive testing using iloprost, results were similar with cardiac catheterization. PVR (149.66 ± 458.01), PVRI (291.12 ± 634.73), SVR (323.04 ± 1057.56) and SVRI (333.25 ± 1467.22) showed remarkable changes from baseline.

Bosentan-related Clinical Worsening

No patient experienced hospitalization, development of right heart failure, worsening pulmonary hypertension or death due to bosentan therapy at week 4, week 8 and week 12 of the study.

Laboratory Parameters

Among laboratory parameters (Table 4), notable differences between baseline and follow-up levels in alkaline phosphatase (26.23 ± 92.37), SGOT (26.31 ± 97.60) and SGPT (16.62 ± 71.26) were observed on the 4th week, while there was a modest change in indirect bilirubin levels (5.20 ± 3.82) on the 12th week

Safety and Tolerability

Respiratory tract infection was one of the medical events experienced by two patients (one from baseline to 12th week of observation period and one on the 12th week follow-up). Three patients experienced headache, one from baseline to 12th week, one on the 4th week only and one on the 12th week follow-up. One patient had edema, another had flushing and one was reported to experience palpitations and hypotension. There was no significant change in liver size observed among the participants.

As shown in Table 5, four patients experienced at least one serious adverse event. One case was assessed as suspected unexpected serious adverse reaction (SUSAR) during the review period: a 23- year old female patient with PAH associated with CHD experienced medically significant headache and numbness of extremities at the time of bosentan up-titration, one month after initiation of the study drug. Following administration of paracetamol, the said medical events resolved within one day while bosentan was continued. The investigators assessed them as related to bosentan.

Another participant experienced medically significant elevation of liver function test (LFT) results (see Table 4) which resolved following drug discontinuation. This was reported as related to bosentan.

One patient experienced medically significant, progressive deterioration of PAH associated with SLE and was hospitalized for fever, cough and abdominal distention. All events were reported as unrelated to bosentan which remained ongoing. The fever, cough and abdominal distention eventually resolved; however, the outcome for PAH deterioration on this patient was not provided.

Another patient underwent prolonged hospitalization due to palpitations and transient decrease in blood pressure (hypotension) following protocol-mandated pulmonary function testing. These resolved while bosentan was ongoing and afterwards reported as a medical event unrelated to the study drug.

One patient experienced a non-serious urinary tract infection (UTI) which was reported as unrelated to bosentan. The outcome was not provided.

One patient was hospitalized and subsequently died due to pulmonary hypertensive crisis following right heart catheterization prior to initiation of bosentan. Following the death of this patient, the protocol and informed consent form of the study were amended to include a new paragraph on the potential risks of right heart catheterization.

Overall, two (15.4%) out of six adverse events were reported as related to the study drug.

At study endpoint, efficacy and safety were assessed. Among 13 patients, 10 (76.9%) considered bosentan as effective while 11 (84.6%) considered it safe. "Effective" was defined as the ability to produce desired results and "safe" was defined as the absence of adverse drug events or minimal adverse drug events.

DISCUSSION

In this post marketing surveillance study, administration of bosentan 125 mg twice daily for 12 weeks generally improved exercise capacity, pulmonary function and cardiopulmonary hemodynamics of the patients involved.

For exercise capacity, remarkable changes were observed in the patients' 6MWD, while there was a small improvement in the Borg dyspnea index and CPET. For WHO functional classification, there was no difference between baseline and 12th week values.

As for pulmonary function parameters, FEV1/FVC, MVV, RV/TLC and sRaw showed modest improvement. For hemodynamic parameters, there was a notable difference in the systolic PAP (by tricuspid jet) compared to baseline.

For cardiopulmonary hemodynamic parameters, PVR, PVRI, SVR and SVRI demonstrated the largest changes both via cardiac catheterization and iloprost.

The results of the study is consistent with other clinical studies^{6,7,9,10} in terms of improvement in 6MWD, mean systolic PAP and pulmonary vascular resistance. However, no statistical test was performed as the sample size (13) was too small to allow for hypothesis testing, therefore limiting the extent to which generalizations can be drawn.

It is interesting to note that lung function abnormalities in PAH while modest and considered less probable to significantly affect patients' symptoms¹⁵ should warrant further attention. Pathophysiological changes in the pulmonary circulation (arterioles and capillaries) begin early in PAH¹⁵ and detectable alterations in cardiopulmonary hemodynamic parameters and manifestation of symptoms usually appear at the late or advanced stage of the disease.^{15,16}

Pulmonary function changes and related respiratory symptoms may be more sensitive to short-term bosentan therapy compared to exercise capacity and cardiopulmonary hemodynamic parameters. Further studies with larger sample size and longer period is recommended to accurately determine the effectiveness of the drug among Filipino patients.

Except for the SUSAR (i.e. headache and numbness of extremities associated with bosentan up-titration), all adverse events reported were consistent with prior studies. Headache with numbness of extremities associated with administration of the study drug is reported for the first time in this study. This underscores the importance of vigilant monitoring of adverse events, especially those that were unexpected and serious, for appropriate intervention and reporting.

Out of 13 patients, 10 (76.9%) considered bosentan as effective while 11 (84.6%) deemed it safe. Liver function test results of the participants were consistent with previous studies. Only one patient necessitated discontinuation of the study drug due to medically relevant elevation of LFT.

CONCLUSION

Bosentan 125 mg administered twice daily generally improved exercise capacity, pulmonary function and cardiopulmonary hemodynamics, with pulmonary function demonstrating the most number of significant results. The drug is generally well-tolerated and effective. However, further studies with larger samples and longer duration is recommended. Bosentan is currently among the useful options for treatment of adult Filipino patients with PAH.

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DISCLOSURE

This post-marketing surveillance study was conducted by Menarini Philippines – Actelion's local partner for the sales and marketing of bosentan – from 5 March 2012 to 25 September 2012 as part of the regulatory requirements under monitored release of bosentan (Tracleer). Actelion was acquired by Johnson & Johnson in 2017, resulting to the transfer of marketing authorization for bosentan in the country from Menarini to Johnson & Johnson (Philippines), Inc. (JJPI) in July 2018. The preparation of this manuscript is supported by both JJPI and Actelion.

Table 1. Demographic and Clinical Characteristics of Patients in the Study

CHARACTERISTIC	Mean $\pm$ SD	No. (%)
Age (years)	34.00 $\pm$ 11.54	
Weight (kg)	47.60 $\pm$ 10.26	
Sex		
Male		1 (7.70)
Female		12 (92.30)
Occupation		
Nurse		1 (7.70)
Student		1 (7.70)
Teacher		1 (7.70)
Unemployed		8 (61.50)
Not indicated		2 (15.40)
Etiology		
Primary (idiopathic) pulmonary hypertension		4 (30.80)
PAH associated with congenital heart defect (CHD)		8 (61.50)
<i>Atrial septal defect (ASD)</i>		1 (7.70)
<i>Patent ductus arteriosus (PDA)</i>		1 (7.70)
<i>Patent foramen ovale (PFO)</i>		2 (15.40)
<i>Ventricular septal defect (VSD)</i>		1 (7.70)
PAH associated with systemic lupus erythematosus (SLE)		1 (7.70)
Pulmonary hypertension associated with other illnesses		0 (0.00)

Table 2. Outcome Measures by Observation Period

OUTCOME MEASURE	NO.	BASELINE Mean $\pm$ SD / No. (%)	WEEK 12 Mean $\pm$ SD / No. (%)	DIFFERENCE Mean $\pm$ SD / No. (%)
Exercise capacity				
6-minute walk distance (m)	12	355.00 $\pm$ 91.01	380.00 $\pm$ 101.45	24.50 $\pm$ 69.66
Dyspnea after 6-minute walk test				
Yes		10 (83.3)		
No		2 (16.7)		
TOTAL		12 (100.0)		
Dyspnea index (Borg scale)	12	2.29 $\pm$ 1.42	1.79 $\pm$ 1.44	0.50 $\pm$ 1.24
Body mass index (BMI)	12	19.46 $\pm$ 2.56	19.46 $\pm$ 2.56	0.00
WHO functional classification				
3.0		12 (100.0)	11 (9.7)	
3.5		0 (0.0)	1 (8.3)	
TOTAL		12 (100.0)	12 (100.0)	
Cardiopulmonary exercise testing (CPET)	10	15.68 $\pm$ 4.78	16.41 $\pm$ 6.59	0.73 $\pm$ 3.53
Arterial blood gas (ABG at room air)				
pH	11	7.47 $\pm$ 0.03	7.45 $\pm$ 0.03	0.02 $\pm$ 0.03
PCO ₂	11	29.89 $\pm$ 3.09	31.10 $\pm$ 4.69	1.21 $\pm$ 4.17
PO ₂	11	77.97 $\pm$ 16.27	76.00 $\pm$ 15.82	1.28 $\pm$ 13.10
BHCO ₃	11	21.33 $\pm$ 2.28	21.16 $\pm$ 2.40	0.16 $\pm$ 3.50
Actual base excess (ABE)	11	-1.02 $\pm$ 2.16	-1.51 $\pm$ 1.93	0.49 $\pm$ 3.33
O ₂ saturation	11	95.27 $\pm$ 2.58	94.69 $\pm$ 3.06	0.58 $\pm$ 2.04

Table 4. Assessment of Laboratory Parameters by Observation Periods

PARAMETER	NO.	BASELINE Mean $\pm$ SD / No. (%)	WEEK 12 Mean $\pm$ SD / No. (%)	DIFFERENCE Mean $\pm$ SD / No. (%)
Alkaline phosphatase				
4th week	13	96.38 $\pm$ 57.09	122.62 $\pm$ 145.42	26.23 $\pm$ 92.37
8th week	12	82.50 $\pm$ 28.66	87.58 $\pm$ 34.87	5.08 $\pm$ 15.78
12th week	12	82.50 $\pm$ 28.66	84.83 $\pm$ 31.84	2.33 $\pm$ 13.92
Liver function test (LFT)				
<i>SGOT (ALT)</i>				
4th week	13	36.77 $\pm$ 20.16	63.08 $\pm$ 114.80	26.31 $\pm$ 97.60
8th week	12	32.00 $\pm$ 11.00	33.08 $\pm$ 13.41	1.08 $\pm$ 9.96
12th week	12	32.00 $\pm$ 11.00	34.42 $\pm$ 8.64	2.42 $\pm$ 7.90
<i>SGPT (AST)</i>				
4th week	13	38.92 $\pm$ 21.76	55.54 $\pm$ 84.29	16.62 $\pm$ 71.26
8th week	12	35.25 $\pm$ 18.03	31.17 $\pm$ 9.51	4.08 $\pm$ 14.56
12th week	12	35.25 $\pm$ 18.03	37.33 $\pm$ 13.23	2.08 $\pm$ 11.23
Bilirubin				
<i>Total bilirubin</i>				
4th week	13	14.68 $\pm$ 9.72	16.32 $\pm$ 8.93	1.65 $\pm$ 8.33
8th week	12	14.68 $\pm$ 9.72	17.43 $\pm$ 10.36	2.75 $\pm$ 5.90
12th week	12	15.04 $\pm$ 10.06	12.46 $\pm$ 5.04	2.58 $\pm$ 7.14
<i>Direct bilirubin</i>				
4th week	13	1.45 $\pm$ 4.19	2.52 $\pm$ 3.89	1.07 $\pm$ 2.28
8th week	12	1.45 $\pm$ 4.19	2.88 $\pm$ 4.52	1.43 $\pm$ 1.62
12th week	12	1.45 $\pm$ 4.19	3.07 $\pm$ 4.33	1.62 $\pm$ 6.24
<i>Indirect bilirubin</i>				
4th week	13	14.22 $\pm$ 5.36	13.42 $\pm$ 6.88	0.80 $\pm$ 6.59
8th week	12	14.59 $\pm$ 5.42	13.78 $\pm$ 7.71	0.82 $\pm$ 4.68
12th week	12	14.59 $\pm$ 5.42	9.39 $\pm$ 6.40	5.20 $\pm$ 3.82

Table 5. Adverse Events Experienced by Study Participants

ADVERSE EVENT	OUTCOME			SERIOUSNESS		
	Total No. (%)	Resolved	Not Indicated	Medically Significant	New Hospitalization	Prolonged Hospitalization
Possibly related to the study drug	2					
<i>Elevated liver function test</i>	1	1	-	1	-	-
<i>Headache and numbness of extremities</i>	1	1	-	1	-	-
Not related to the study drug	4					
<i>Serious progressive deterioration of PAH secondary to SLE</i>	1	-	1	1	-	-
<i>Urinary tract infection</i>	1	1	-	-	-	-
<i>Fever and cough</i>	1	1	-	-	1	-
<i>Palpitation and hypotension</i>	1	1	-	-	-	1
EVENT RATE	6 (46.2)					
EVENT RELATED TO STUDY DRUG	2 (15.4)					

*PAH, Pulmonary arterial hypertension; SLE, systemic lupus erythematosus

Amalgamating Osteotomy: A Novel Surgical Technique for the Reconstruction of Bilateral Preaxial Polydactyly of the Foot*

Al-Mondjid L. Lee, MD¹

Leonard T. Khu, MD²

Abstract

Introduction: Polydactyly of the foot is not uncommon, with the preaxial type or hallux duplication comprising 15% of cases.² Metatarsal type preaxial polydactyly (MTPP) accounts for an estimated third of all reported preaxial polydactyly cases. Traditional surgical procedures for this condition frequently have drawbacks that include varying degrees of hallux varus and a bigger forefoot.¹ Due to these disadvantages, developed a simple and effective technique for the reconstruction of MTPP.

Case Report: Amalgamating osteotomy procedures were done for bilateral MTPP in an 18-month old girl who had been experiencing shoe wear difficulty. An excellent and pain-free functional outcome was achieved with good cosmetic appearance and an improved ability to wear various kinds of footwear.

Conclusion: Amalgamating osteotomy could be the procedure of choice for the reconstruction of metatarsal type preaxial polydactyly. Case series and long-term follow-ups should be done to compare outcomes with other surgical techniques.

Keywords: polydactyly, foot deformity, amalgamating osteotomy, foot reconstructive surgery

*1st Place, 2019 Philippine Medical Association Case Report Presentation Contest, May 15, 2019

¹Resident, Department of Orthopedics, Northern Mindanao Medical Center

²Consultant, Department of Orthopedics, Northern Mindanao Medical Center

INTRODUCTION

Polydactyly of the foot is characterized by extra toes, with the duplication either at the phalangeal level only or may include the metatarsal. Polydactyly may be preaxial (medial), central, or postaxial (lateral).² Due to the added number of toes, difficulty with shoe wear, pain, and even soft tissue trauma may be present and surgical treatment is often advised.³

Compared to duplication of the digit only, surgical treatment of polydactyly with digit plus metatarsal involvement may pose more difficulties.³ Cases of metatarsal type preaxial polydactyly (MTPP) are particularly challenging, as measures to prevent residual hallux varus and maintain a stable 1st metatarsotarsal joint and medial longitudinal arch should be considered.¹ Unfortunately, traditional surgical reconstruction techniques for MTPP have shown inconsistent results, occasionally leading to additional surgery or an unsatisfactory clinical outcome.^{4,5,6}

Amalgamating osteotomy, a new surgical treatment for MTPP, takes these important factors into consideration and allows for uncomplicated longitudinal growth in the pediatric population.¹ More importantly, it is a simple bone and soft tissue procedure that can easily be taught to and practiced by most surgeons around the world. A thorough search of published reports shows that this procedure could be the first of its kind done in the Philippines.

MATERIALS AND METHODS

This was a case report of a noble surgical procedure, amalgamating osteotomy as described by Boyle et.al., in the treatment of a child with MTPP; included are the description and illustration of the surgical technique and clinical outcome of the patient after a year of surgery.

Surgical Technique

The amalgamating osteotomy is indicated in children who present with MTPP with a hypoplastic lateral metatarsal, a stable medial MTT joint, and a cosmetically near-normal lateral hallux.¹

A zigzag incision is placed on the medial border of the foot (fig. C1), around the medial hallux to construct a nonlinear scar that will not retract and potentially cause hallux varus. Full-thickness subcutaneous dorsal and plantar flaps are elevated. Abductor hallucis is detached distally from the medial hallux and maintained as a muscular flap (fig. C2). The extensor hallucis longus tendon to the medial hallux is transected, and the space between the medial and lateral hallux metatarsals is developed; the metatarsal heads may have a cartilaginous connection not evident on preoperative radiographs. The tarsometatarsal ligaments of the hypoplastic lateral hallux metatarsal are transected. The medial hallux metatarsal is then osteotomized obliquely and distal to the physis (fig. C3). The medial neurovascular bundle is ligated and divided, the medial flexor tendons are divided, and the medial hallux is dissected free from the lateral common digital nerve and discarded. A plantar flap of medial skin is preserved to facilitate later wound closure. The lateral hallux metatarsal is then osteotomized obliquely (fig. C4) at a position that matches the medial metatarsal osteotomy and produces a cosmetic first metatarsal length when the 2 metatarsal remnants are combined (fig. C6). The distal portion of the lateral hallux metatarsal is then impaled into the medullary canal of the medial metatarsal remnant, with the amalgamating osteotomy stabilized with a single Kirschner wire (fig. C7). The periosteum is closed over the osteotomy site and the abductor hallucis is transferred to the remaining hallux. The skin flaps are closed (fig. C8) and an above knee mold is applied. The cast and wire are removed 8 weeks postoperatively.

FIGURE C.

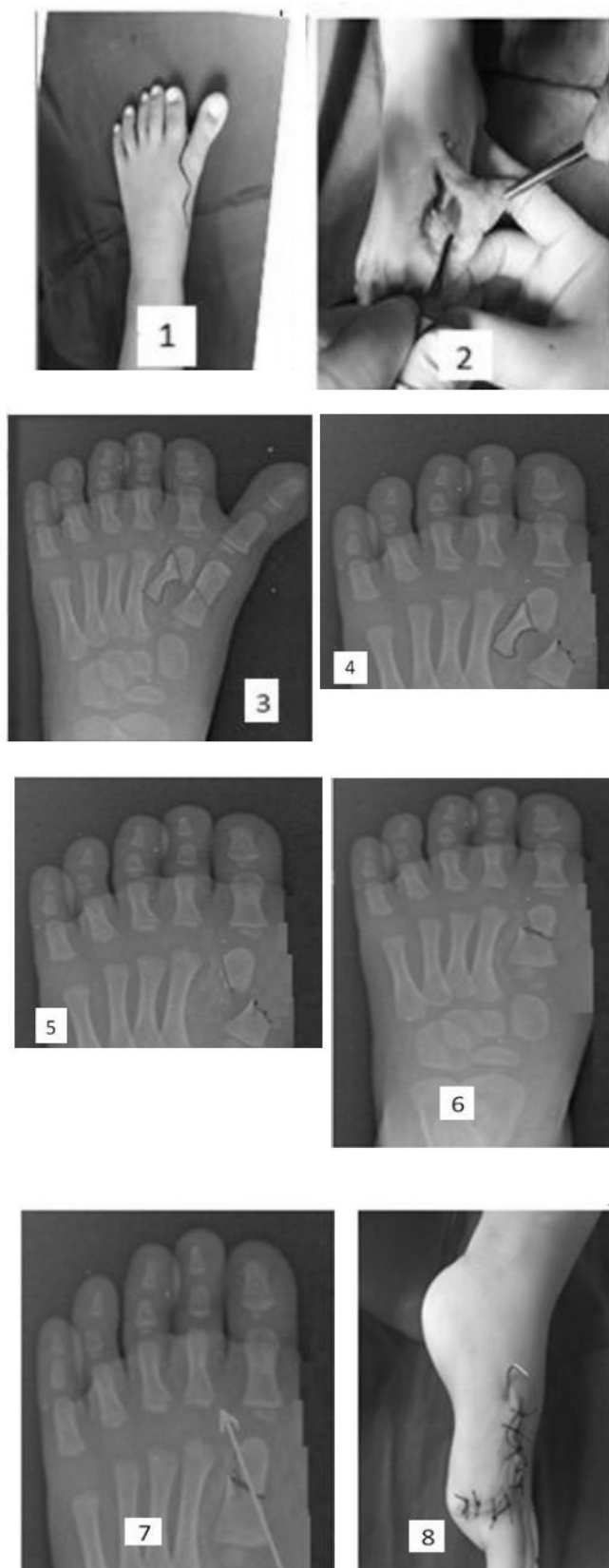


FIGURE C. Stepwise illustration to show how amalgamating osteotomy is done: 1. Medial zigzag incision to expose the duplicated metatarsals; 2. Flap made from the remaining soft tissues; 3. Red lines demonstrate suitable metatarsal osteotomy locations; osteotomize and excise medial hallux and distal medial ray; 4. Osteotomize and excise proximal part of the hypoplastic ray; 5. Remnants of medial and lateral 1st ray after excision; 6. Amalgamate or unite the remnants of both medial and lateral 1st rays. 7. Kirschner wire inserted between the amalgamated remnants; 8. Flap closed layer by layer.

Postoperative Outcomes

In this case report, similar to the study by Boyle et. al in 2016, clinical outcomes for our patient were evaluated using Phelps and Grogan outcome scale. Under this scale, an excellent foot has no pain, no shoe wear issues, no significant residual deformity, and a cosmetically acceptable appearance; a good foot has occasional pain, difficulty with some shoe styles, or minimal residual toe deformity; a poor foot has constant pain, marked shoe-wear difficulty, or substantial deformity of the residual toes.

CASE REPORT

This is the case of an 18-month old girl, the youngest among four children of healthy, non-consanguineous parents. At least three generations of the family on the paternal side has either hand or foot polydactyly or other isolated hand or foot malformations. Her father and siblings also have hand or foot polydactyly but no other associated malformations. Since local belief considers polydactyly as a sign of good fortune, and perhaps since no accessible treatment was then available, no one else in the family has undergone surgery for the condition.

Patient PZ was brought by her parents to the Orthopedics outpatient clinic last October 2017 with the hope of possible treatment for her polydactyly. The parents wanted PZ to undergo reconstructive surgery to prevent possible bullying and psychological consequences later on. They noticed that since PZ started walking at 9 months of age, she has had difficulty wearing shoes, often complaining of intense pain, swelling and sometimes skin trauma. Furthermore, it was noted that the patient has been experiencing repeated falls especially during fast strides as her right and left big toes come in contact during these times, causing her to lose balance and fall.

Physical examination revealed bilateral foot polydactyly, with 6 toes on each foot (fig. A). Other than these findings there were no other malformations or abnormal conditions noted after intensive investigation.



FIGURE A. Right and left foot of PZ, an 18-month old female, showing 6 toes on each foot with an obvious medial hallux varus and a cosmetically near-normal lateral hallux.

X-rays of the right and left foot (fig. B) show an extra digit with an underdeveloped metatarsal between the normal 1st and 2nd digits. Its accompanying phalanges appear to be duplications of the normal 2nd digit. Findings are the same on both sides. Bone density is normal.

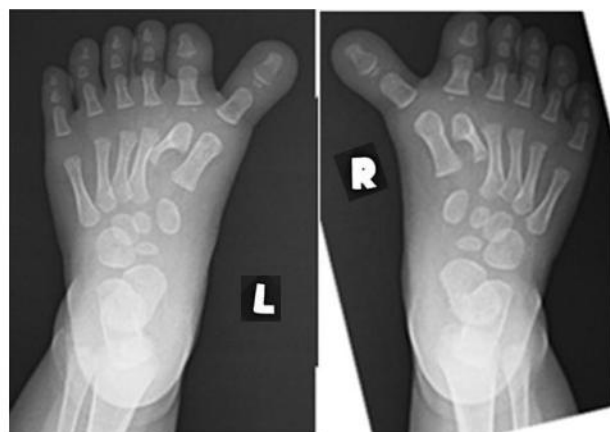


FIGURE B: Initial anteroposterior (AP) plain radiograph of the right and left foot of PZ, an 18-month old female, showing bilateral hypoplastic lateral 1st metatarsal and a bilateral varus deformity of medial 1st metatarsal

RESULTS AND DISCUSSION

Patient PZ underwent the first amalgamating osteotomy for MTTP in the Philippines last November 2017. Patient was 18-month old at the time of operation which included the left and right foot. PZ had preaxial MTTP of both feet with near-normal lateral hallucis. Other PE findings were unremarkable. On plain radiography, she has bilateral stable first MTT joints and hypoplastic lateral rays.

PZ underwent reconstructive surgery for her MTTP using amalgamating osteotomy as the main technique. Intraoperatively, the patient was placed under general anesthesia and tourniquet was applied to the extremity. Total operative time was 2 and half hours with minimal blood loss. Eight weeks post-surgery, bone healing by callus formation was seen on x-ray (fig. E1). The wound was clean and dry. The pin was removed at this time and the patient was allowed to bear weight as tolerated. Fifteen months after surgery, the patient displayed an excellent functional outcome based on Phelps and Grogan clinical outcome scale. Plain radiographs (fig. E2) showed a remodeled osteotomy, well-aligned first ray, no growth disturbance, no hallux varus. There were no complications, with note of only a minor surgical site scar (fig. G). Patient has no shoe wear problem and has been wearing her different styles of footwear (fig. F) and can walk and run on different terrains (fig. H).





FIGURE E. Plain x-rays AP view of right and left foot. 1, 8th weeks Postoperative radiograph shows that the amalgamated remnants secured with a single Kirschner wire. 2, Radiograph at 65 week, displays healed bone with no hallux varus deformity.

Phelps et. al., (1985), concluded that in patient with preaxial polydactyly, particularly when there is hallux varus, nonoperative management of is generally not effective, shoe wear problems and foot pain are usually present.

Aside from cosmetic issues with potential psychosocial impacts, shoe wear difficulties at the onset of walking age are to be expected. That extra digit and extra ray increases the width of the forefoot making the usual shoes made for 5-toed people very fitting or tight, causing continuous friction and shearing forces aggravated by walking. This leads to swelling, erythema, abrasion and perhaps even more severe soft tissue trauma. Surgery is indicated in these instances.

Surgical options for patients with preaxial polydactyly with an associated hallux varus deformity include the McElvenny procedure, the Farmer procedure, and amalgamating osteotomy, which were introduced in 1941, 1958, and 2016, respectively.

In both Farmer and McElvenny procedures, the lateral or the near normal hallux is resected then extensive soft tissue reconstruction is done, leaving both metatarsals in place. The difference between the two procedures is the technique used to prevent medial hallux varus. In Farmer, it is the extensive reconstruction of soft tissues, muscle

and rotational flap while in McElvenny it is the use of a k-wire that is inserted longitudinally at the 1st metatarsophalangeal joint. As the patient grows, both lateral and medial 1st ray increase in length and width as with the remaining rays, leading to a bigger forefoot and an obvious hallux varus.

These drawbacks have led to the development of a new surgical reconstructive technique for MTPP, the amalgamating osteotomy.¹ It provides a technically simple method that takes advantage of combining a stable medial MTT joint with the cosmetically acceptable lateral hallux, thus maintaining the medial longitudinal arch of the foot. The arch is vital for shock absorption during ambulation while limiting the possibility of a potential recurrent hallux deformity and allowing for ongoing longitudinal growth.

Boyle has reported excellent functional results in two patients using the Phelps and Grogan clinical outcome scale. Similarly, in this case report, the use of amalgamating osteotomy in the treatment of bilateral MTPP in a child with hypoplastic lateral metatarsals and clinically acceptable lateral hallucis resulted in an excellent outcome.

CONCLUSION

Metatarsal type preaxial polydactyly and its attendant problems can be managed surgically using a simple and effective amalgamating osteotomy procedure. This may be of particular importance in local settings where the inadequacy of knowledge about the condition and limited resources would preclude the choice of technically demanding surgeries or multiple procedures for residual problems.

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FIGURE F: Patient using varied footwear



FIGURE G: Gross pictures of right and left foot; 1, after removal of pin at 8 weeks post-op showing 5 digits on each foot with scar formed at surgical site; 2, seven months after surgery, no hallux varus deformity noted and an apparent decrease prominence of scar on both feet.



FIGURE H: Patient walking on different terrains

Sinonasal Ameloblastic Carcinoma in a 48-year-old Filipino Male: A Rare Fortuity*

Jules Verne M. Villanueva, MD¹

Abstract

Objective: To report a case of sinonasal ameloblastic carcinoma in a 48-year-old Filipino male & discuss its clinical manifestations, diagnosis, histopathology and possible treatment options.

Methods: Design: Case Report, Setting: Tertiary Government Hospital, Patient: One

Results: A 48-year-old Filipino male consulted at our OPD due to progressive right-sided nasal obstruction, rhinorrhea, hyposmia & intermittent controlled episodes of epistaxis for one year. On anterior & posterior rhinoscopy, a fleshy, soft tissue mass is seen in the nasal floor. On further examination with rigid nasal endoscopy, the same pink, fleshy, soft tissue mass was seen occupying entirely the right nasal floor with nasopharynx hardly to be visualized, and friable upon insinuation. A preoperative punch biopsy of the mass was done at our OPD revealing histologic features consistent with ameloblastoma. Contrast-enhanced computed tomography (CT) scan of the paranasal sinuses revealed a prominent soft tissue density mass lesion filling right sinonasal cavity. It is further noted the heterogenous characteristic of an isodense mass in the right nasal cavity enhancing from the nasopharyngeal area, with complete obstruction of the osteomeatal unit (OMU) and some lytic changes on the medial maxillary sinus wall however no bony changes noted on bilateral orbital floor and skull base. The mass was completely excised by medial maxillectomy via midfacial degloving. Final histopathologic studies showed islands of lace-like areas and nests of atypical odontogenic cells with central stellate reticulum, palisading columnar cells exhibiting reverse polarity and moderate mitotic activity with atypical mitotic figures present on two specimens labelled as "posterior nasal septal mass" & "nasopharyngeal mass".

Conclusion: Ameloblastic carcinoma is an uncommon entity of malignant odontogenic tumors that may originate *de novo* or from a benign ameloblastoma which exhibits malignant histologic features in the primary lesion and/or distant metastasis. On the other hand, malignant ameloblastoma exhibit benign histologic features both for the primary and distant metastasis. This report depicted an uncommon case of ameloblastic carcinoma found extragnathically, that is in the sinonasal region. This is the second case of ameloblastic carcinoma of the sinonasal region documented in the Philippines. This case report might be a step on the ladder to generate more information regarding the biologic behavior of this entity and might ignite the enthusiasm in performing more evidence-based studies needed for its treatment as well as for its surveillance. Wide surgical resection, which is the treatment of choice, can pose challenge to otolaryngologist in the case of sinonasal ameloblastic carcinoma due to the surrounding vital structures present. Role of chemotherapy and radiotherapy is as yet conclusive due to very limited evidence-based studies available.

Keywords: sinonasal ameloblastoma, ameloblastic carcinoma, sinonasal ameloblastic carcinoma

*2nd Place, 2019 Philippine Medical Association Case Report Presentation Contest, May 15, 2019

¹Resident, Dr. Paulino J. Garcia Memorial Research and Medical Center, Cabanatuan City, Nueva Ecija

INTRODUCTION

Ameloblastoma is a common benign locally aggressive odontogenic epithelial tumor with slow growth, usually arising in the mandible or maxilla. An entity with high propensity for recurrence that are believed to be remnants of odontogenic epithelium, lining of odontogenic cysts, and the basal layer overlying oral mucosa.¹ Suggested sources for odontogenic epithelium are cell rests of the dental lamina, a developing enamel organ, the lining of odontogenic cyst, basal cells of oral mucosa, or heterotopic embryonic organ epithelium.¹

Although it is the most common true odontogenic neoplasm with an incidence of 11%, only 1% comprises all head and neck tumors.² The estimated incidence of ameloblastoma is approximately 0.5 per million populations per year.³ Approximately 80% of ameloblastoma occur in the mandible and roughly 15-20% as growing masses in the maxilla.² Majority of the case reports documented regarding ameloblastoma arising within the sinonasal cavity are found to have originated from the maxilla. However rare case reports document true primary sinonasal ameloblastomas without connections to gnathic sites.

With the rarity of ameloblastoma arising primarily from the sinonasal cavity, malignant variants are exceptionally rare. It accounts for 1.5% to 2% of all odontogenic tumors. The largest population-based series of malignant ameloblastoma & ameloblastic carcinoma conducted by Rizzitelli et al. revealed an overall incidence of 1.79 per 10 million person/year. The study also showed a male predilection with a ratio of 1.59:1 and apparently significantly higher incidence among blacks.⁵ In the past, terms malignant ameloblastoma and ameloblastic carcinoma have been used interchangeably for this variants, however a distinction has been made wherein malignant ameloblastoma tends to metastasize in spite of the benign histology while ameloblastic carcinoma exhibit features of both ameloblastoma and carcinoma with or without metastasis. It may arise *de novo* or from transformation of a long-standing primarily benign lesion which has undergone several excisions.⁴ Ameloblastic carcinoma can be further divided into two subtypes: primary or secondary. Primary ameloblastic carcinoma arises *de novo*, while secondary ameloblastic carcinomas are a result of

malignant transformation of a previously diagnosed benign ameloblastoma.⁵ Swelling of the involved site is the commonest manifestation of patient with maxillary involvement of ameloblastic carcinoma.⁷

To date, only one study has been published regarding sinonasal ameloblastic carcinoma in the country, wherein the author described a 50-year-old Filipino woman with a previous reported diagnosis of sinonasal ameloblastoma underwent Endoscopic Sinus Surgery last July 2010 and was lost to follow up thereafter. She experienced recurrence of unilateral, right-sided epistaxis with associated right-sided nasal obstruction last December 2012 and finally consulted on March 2013 wherein a fleshy mass was seen in the right nasal cavity. Total maxillectomy with right orbital exenteration and prosthetic reconstruction was done last July 2013 consistent with the diagnosis of ameloblastic carcinoma on histopathologic examination. Further surgery was done to address positive margins at the superior & inferior margins of the resection area as well as the ethmoids and inferior orbital wall. Intraoperatively, tumor in the superior ethmoid area was positive for ameloblastic carcinoma on frozen section. Bare bone excision was attempted with tumor noted in the area of the cribriform plate. Further work up revealed hepatic and pulmonary metastases hence several cycles of chemotherapy was delivered. The patient died after two years of treatment.⁶ This represent a secondary type of ameloblastic carcinoma in relation with the previously cited literature. In contrast with the patient in this study, the histopathologic diagnosis after the definitive surgery (i.e. right medial maxillectomy via midfacial degloving) was an outright ameloblastic carcinoma. This can be a case of ameloblastic carcinoma arising *de novo*.

Aside from the extreme rarity of ameloblastic carcinoma's occurrence in the gnathic site, this report made it more uncommon since the patient's ameloblastic carcinoma in this case report was found extragnathically, that is in the sinonasal area. Thus, this deserves high academic interest.

CASE REPORT

A 48-year-old Filipino male presented in our hospital with seven months history of progressive right-sided nasal obstruction with associated rhinorrhea, and frontonasal headache. He had a history of intermittent controlled epistaxis and hyposmia then subsequently proceeding to anosmia three months prior to admission. Past medical history of previous self-dental extractions from various years ago was also noted from the patient. There is no history of visual defect (i.e. diplopia, ptosis), atopy or previous trauma to the nose. His weight was stable and his general health was satisfactory.

Upon inspection of the oral cavity, missing teeth were noted (numbers 15, 16, 17, 30 & 32) as these were the teeth he extracted by himself from various years ago. The hard & soft palates are without lesions, bleeding and/or bulge/mass. Upon anterior rhinoscopy, a pink, fleshy, soft tissue mass was seen in the nasal floor with associated foul-smelling, mucoid rhinorrhea with the same mass noted on posterior rhinoscopy. Otoscopy of both ears showed intact tympanic membrane with no noted retractions or opacifications. Tuning fork tests (i.e. Weber and Rinne Tests) were unremarkable. Diagnostic rigid nasal endoscopy of the right nasal cavity (Fig. 1) revealed a pink, soft, fleshy, ill-defined mass occupying entirely the nasal floor that easily bleeds upon manipulation. The nasopharynx was not appreciated due to mass obliteration even with insinuation. Also in the same nasal cavity, a pale, glistening, grape-like grade 2 polypoid mass (Fig. 2) was seen attached to the lateral nasal wall. Nasal endoscopy of the contralateral nasal cavity revealed unremarkable result except for the presence of the same mass as previously described in the right nasal floor, seen in the nasopharyngeal area but not completely obliterating it.

A preoperative contrast-enhanced computed tomography (CECT) of the paranasal sinuses (PNS) was done. A representative CECT axial cut of PNS (Fig. 3a) demonstrated a prominent large, ill-defined heterogeneously enhancing isodense mass occupying the right nasal cavity extending to the nasopharyngeal area measuring 3.8 x 3.5 x 3.6 cm with associated multiple hyperdense materials thought to be part of the tumoral calcifications. The mass is noted obstructing the right ostiomeatal unit (OMU) with associated

air-fluid level and some lytic changes seen in the medial maxillary sinus wall (Fig. 3b). Lateral pterygoids are without lytic changes. Contralateral nasal cavity and maxillary sinus is unremarkable. Representative coronal cut of the PNS CECT (Fig. 4) depicted extension of the isodense mass on bilateral ethmoids and sphenoid sinuses. No lytic change was observed on the cribriform plate and bilateral orbital floors. On sagittal cut (Fig. 5), the mass is seen enhancing from the nasopharyngeal area with extension to anterior & posterior ethmoid sinuses and sphenoid sinus. Frontal sinus is well aerated with no noted lytic changes in skull base or intracranial extension.

A preoperative punch biopsy was done showing minute pieces of tan to dark brown irregular soft tissues measuring 1.5 x 1.5 x 0.5 cm in aggregate. On light microscopic examination (Fig. 6), low power view showed a micrograph shedding two distinct histologic findings, that is the presence of inflammatory nasal polyp (Fig. 7a) lined by a respiratory epithelium (i.e. pseudostratified columnar ciliated epithelium) with neutrophils & lymphocytes scattered in a background of myxoid stroma while the second histologic finding labeled as a "suspicious fragment" (Fig. 7b) demonstrated an odontogenic epithelium with conspicuous calcifications (consistent with the hyperdense material noted in the CECT of the PNS). On further investigation of the "suspicious fragment" in high power view (Fig. 8 & 9), it revealed islands of cells presented predominantly follicular histologic pattern resembling enamel organ epithelium with stellate reticulum at the center. Peripheral palisading columnar cells are seen exhibiting *Reverse Polarization*. This was signed out as a case of ameloblastoma. Patient underwent excision of the mass with medial maxillectomy, right via midfacial degloving. Intraoperatively, a pink, fleshy, soft tissue, irregularly-shaped mass was noted along the nasal floor up to the nasopharynx and posterior nasal septum with no noted extension into the right maxillary sinus. Only mucous secretions are noted and suctioned in the maxillary, ethmoids and sphenoid sinuses. Three separate tissue samples (Fig. 10a, 10b, 10c) were sent to Anatomic Laboratory for histopathological diagnosis. Section of the specimen labeled "right lateral nasal mass" (Fig. 10a) show fragments consistent with polyp and fragments of benign nasal mucosal epithelium admixed with unremarkable bony fragments.

Sections of the specimen labeled "posterior septal nasal mass" and "nasopharyngeal mass" (Fig. 10b & c respectively) revealed fragments of a malignant mesenchymal neoplasm. The tumor cells are arranged as nodules to elongated structures of atypical odontogenic epithelium with central stellate reticulum (Fig. 11). On HPO, odontogenic epithelium is seen lined by peripheral palisading columnar cells exhibiting *reverse polarization* with polyhedral cells at the center (Fig. 12). Microscopic characteristics of carcinoma were also present as demonstrated on HPO, depicting island of focal lace-like areas and nests of moderately atypical odontogenic cells with large ovoid nuclei, coarse chromatin, and prominent nucleoli with associated moderate mitotic activity and atypical mitotic figures (Fig. 13). This was signed out as Ameloblastic Carcinoma with specimens labeled as "posterior nasal septal mass" and "nasopharyngeal mass" while Inflammatory Polyp for specimen labeled as "right lateral nasal mass".

After learning the result of the histopathology, series of metastatic work-up were done both for the laboratory and radiologic exams. Liver profile test result is within the normal range. Neck CT Scan with contrast showed no nodal metastasis. Other radiologic studies include cranial, chest and abdominal CT scan which revealed unremarkable results.

The postoperative course was uncomplicated and the patient was eventually discharged improved after two hospital days. Nasal packing was kept in place and was removed after five days.

DISCUSSION

Ameloblastoma is a locally aggressive epithelial-derived odontogenic tumor with benign histologic components that exhibit a high recurrence rate if surgical resection is not adequate. The malignant forms of ameloblastoma have been controversial for many years. Before, malignant ameloblastoma and ameloblastic carcinoma have been used interchangeably. However, a delineation have been made between the two wherein the former has the ability to metastasize despite its benign histology in either/both the primary and/or the metastatic lesion while the latter demonstrates histologic features of both ameloblastoma and carcinoma regardless of the presence of metastasis.⁸ As

in the representative slides of the patient (Fig. 10), lace-like areas and nests of moderately atypical odontogenic epithelium with central stellate reticulum are noted. Features of carcinoma like the presence of odontogenic cells with large ovoid nuclei, coarse chromatin and prominent nucleoli were also seen. Other features suggestive of malignancy are the presence of moderate mitotic activities with atypical mitotic figures in the micrograph.

They are extremely rare malignant odontogenic epithelial neoplasm that may arise *de novo* or from a pre-existing benign odontogenic lesion accounting for 1.5% to 2% of all odontogenic tumors. The overall incidence rate of these ameloblastic carcinomas was 1.79 per 10 million person/year.⁵ The commonest involved area is the mandible (i.e. the posterior portion of the mandible).⁷ It occurs in a wide range of age groups. Male population is more affected than that of the female in a 1.59:1 ratio and showed a higher incidence among black population.⁵ Usual presenting manifestation is swelling of the involve area and others have associated pain, rapid growth, trismus and dysphonia.⁷

Aside from the rarity of the malignant variants of ameloblastoma, extragnathic ameloblastic carcinoma arising primarily from the sinonasal region is extremely uncommon. To the best of my knowledge, there are no statistical figures yet regarding the incidence rate of ameloblastic carcinoma arising primarily from the sinonasal region. Review of literatures reveals reports and incidence of primary benign sinonasal ameloblastoma but not for their malignant counterpart. Only one case report has been published in the country regarding this rare malignant entity. del Mundo⁶ described a 50-year-old patient with an initial diagnosis of extragnathic soft tissue ameloblastoma who subsequently lost to follow up and came back for consult after three years after experiencing the same symptoms (right-sided epistaxis and nasal obstruction) prior to the first surgery (i.e. endoscopic sinus surgery). Total maxillectomy with right orbital exenteration & prosthesis reconstruction was done revealing histopathologic features consistent for ameloblastic carcinoma. This is believed to be a malignant transformation arising from a benign lesion, contrary to the finding of the largest comprehensive literature published by Schafer et al., wherein no malignant transformation was accounted among the 24 cases of ameloblastoma arising exclusively in the sinonasal tract from the

20,000 sinonasal tumors for over 40 years.¹¹ However, the patient in this case revealed a histopathologic diagnosis of an outright ameloblastic carcinoma that is thought to be a product of a *de novo* process. This is in contrary to the published report of del Mundo.⁶

The embryologic development of the sinonasal tract and odontogenic apparatus is closely related. The sinonasal tract arises from the ectodermally derived nasal pits that invaginate to cover the oronasal membrane, conchae, primary and secondary palatine processes, and diverticula of the lateral nasal wall. The odontogenic apparatus is a combination of an endophytic proliferation of the basal layer of the ectodermally derived mesenchyme. Although hypothetical, it appears quite likely that this embryologic approximation allows the sinonasal tract mucosa either to incorporate odontogenic epithelium or to acquire cells capable of odontogenesis during development.^{9,10}

Schafer *et al.* stated that extragnathic ameloblastomas may have arisen ectopically or a misplaced odontogenic rests.¹¹ Moreover, Bakay¹² proposed the basal cell layer of the surfaced epithelium as the origin of these extragnathic ameloblastoma. Other author like Woo *et al.* suggested that the possible origins of extragnathic ameloblastomas are from the pluripotential cells in the basal layer of the buccal mucosa. Of interesting account is that sinonasal ameloblastomas can occur after some inductive process on the sinonasal epithelium that results in the neoplastic transformation of retained or acquired odontogenic cells towards ameloblastomatous differentiation. The presence of chronic sinusitis and squamous metaplasia in the areas adjacent to the ameloblastoma could be that initiating event.¹¹ In relation to our patient, he presented with chronic sinusitis and nasal endoscopy findings revealed chronic inflammation, that is the presence of nasal polypoid, could be the initiating event.

No pathognomonic radiographic findings yet were documented for ameloblastic carcinoma due to its rarity although, they appear with aggressive presentation. Conventional multilocular and radioluscent ("soap bubble") appearance was

not seen in the patient in this report in contrast with their gnathic counterpart but showed an enhancing heterogeneous isodense lesion with aggressive presentation of conspicuous calcifications and lytic changes (i.e. medial maxillary sinus wall). A definitive tissue biopsy is hence required in the diagnosis of ameloblastic carcinoma.

Microscopically, the histomorphologic features of extragnathic sinonasal ameloblastomas mirror their gnathic counterparts which include sheets of odontogenic epithelium.¹² The epithelium is composed of a peripheral palisading and hyperchromatic nuclei oriented away from the basement membrane (known as *reverse polarization*) and centrally placed stellate reticulum with loosely arranged cells surrounded by a supporting stroma compatible with the diagnosis of ameloblastoma, both for gnathic and extragnathic variants. Furthermore, ameloblastic carcinomas have these characteristics with histologic evidence of carcinoma. Patient's histopathology in the report revealed histopathologic findings consistent with ameloblastoma with features of carcinoma (i.e. odontogenic cells with large ovoid nuclei, coarse chromatin, prominent nucleoli and atypical mitotic figures).

Controversy still exists regarding its treatment due to the lack of evidence-based study particularly studies dealing with the ameloblastic carcinoma arising exclusively in the sinonasal region. Surgery is the treatment of choice for its gnathic counterpart with an en bloc removal of 1-2 cm of normal bone. Surgical resection is the mainstay treatment for sinonasal ameloblastic carcinoma however the extent of the resection may be limited related to adjacent pivotal anatomical structures. Neck dissections should only be performed for clinically positive lymph nodes.¹³

Authors have doubt on the effectiveness of radiotherapy since it is considered a radioresistant tumor. But Atkinson *et al.*,¹⁴ retrospectively reviewed 10 patients with ameloblastomas treated with megavoltage irradiation and concluded that ameloblastoma is not an inherently radioresistant tumor. Recommended treatment dosages are between 3,000 cGy and 5,000 cGy.

Chemotherapy does not appear to have a role in ameloblastoma. Results of such treatment for non-metastatic disease have been poor however in the setting of metastatic disease, Ramadas et al. found the use of cisplatin, adriamycin and cyclophosphamide to be beneficial.¹⁵ Due to the limited evidence-based studies, the role of radiotherapy and chemotherapy is as yet conclusive.

The median survival was 17.6 years from the time of diagnosis and increasing age was associated with a statistically significant poorer survival.⁵ Recurrence of ameloblastic carcinomas locally vary from 0.5 – 11 years after definitive therapy.¹⁶ Dissemination may result from multiple recurrences or repeated surgical procedures for the treatment of these recurrences causes implantation of tumor cells into the blood or lymphatic vessels. The most common site of metastasis is the lung followed by the bone, liver and brain. Distant metastasis can occur in the absence of a local or regional recurrence.¹⁷ However once metastases occurred, the median survival was 2 years.¹⁸

CONCLUSION

This report depicted an uncommon case of ameloblastic carcinoma found extragnathically, that is in the sinonasal region. Clinical manifestations are non-specific such as rhinorrhea, nasal obstruction, hyposmia and epistaxis. Diagnosis is mainly by histopathology. Unlike with their gnathic counterparts, radiologic findings for sinonasal ameloblastic carcinoma are not pathognomonic, wherein local invasion such as lytic changes and calcifications can be observed. This only shows that ameloblastoma can show a variety of histologic & biologic behavior ranging from benignity to frank malignancy. This is the second case of ameloblastic carcinoma of the sinonasal region documented in the Philippines. This case report might be a step on the ladder to generate more information regarding the biologic behavior of this entity and might ignite the enthusiasm in performing more evidence-based studies needed for its treatment as well as for its surveillance. Surgical resection is still the treatment modality for ameloblastic carcinoma, with neck dissection if with evidence of nodal metastasis. Patients with ameloblastic carcinomas should undergo active surveillance or a life-long judicious follow-up including regular CT or MRI scan for early detection of recurrence.

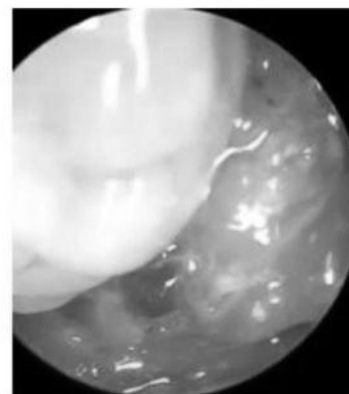


Fig 1: Nasal endoscopy of right nasal cavity showing a pink, soft, fleshy, ill-defined, friable mass completely obliterating the nasal floor

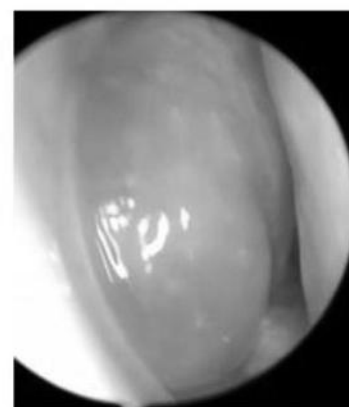


Fig 2: Nasal endoscopy of right nasal cavity showing a pale, glistening, grape-like, grade 2 polypoid mass attached to the lateral nasal wall



Fig 3a: Axial CECT scan of PNS showing a large, ill-defined heterogenous isodense mass occupying the right nasal cavity with multiple hyperdense material



Fig 3b: Bone window of Axial CECT scan of PNS with evident lytic changes on right medial maxillary sinus wall



Fig 4: Coronal CECT scan of PNS showing the extent of the mass to bilateral ethmoid & sphenoid sinuses



Fig 5: Sagittal CECT scan of PNS showing the extent of the mass enhancing from the nasopharynx to the nasal cavity, ethmoids & sphenoid sinuses

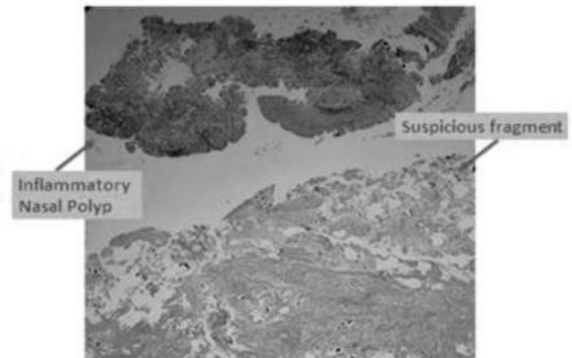


Fig 6: Light Microscopy (LPO) depicting two different histologic findings in one specimen showing an "Inflammatory Nasal Polyp" & "Suspicious Fragment"

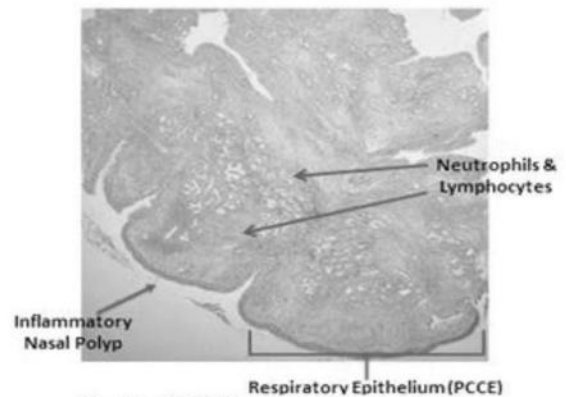


Fig 7a: Light Microscopy (LPO) showing the epithelial lining of a nasal polyp with admixed neutrophils & lymphocytes

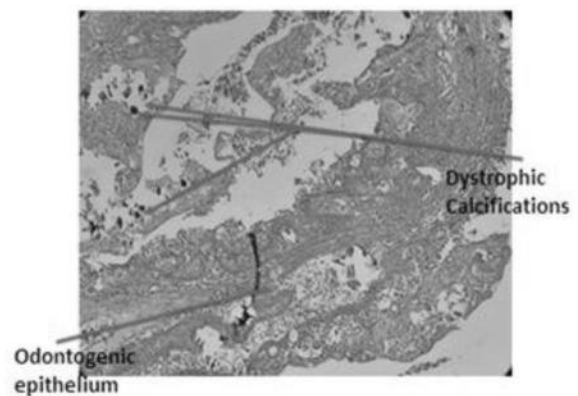


Fig 7b: Microphotograph (LPO) of "suspicious fragment" demonstrating an odontogenic epithelium with conspicuous calcifications

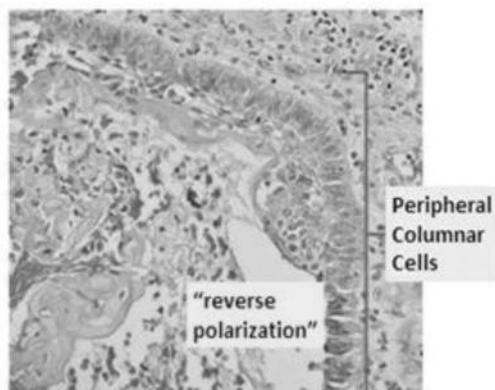


Fig 8: High power view of the "suspicious fragment" showing peripheral palisading columnar cells exhibiting "reverse polarization"

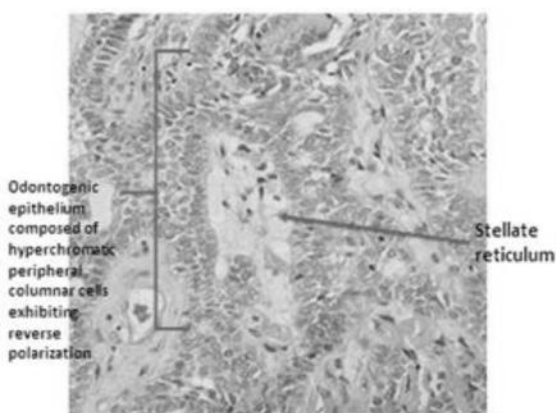


Fig 9: High power view of the "suspicious fragment" showing hyperchromatic peripheral palisading columnar cells in "reverse polarity" with centrally located stellate reticulum



Fig 10b: Posterior nasal septal mass consisting of few fragmented pieces of dark brown, rubbery tissues measuring 2.0 x 1.5 x 0.5 cm



Fig 10c: Nasopharyngeal mass consisting of few fragmented pieces of brown, soft tissues measuring 3.0 x 2.0 x 1.0 cm in aggregate



Fig 10a: Right lateral nasal mass consisting of few fragmented pieces of dark brown, rubbery tissues admixed with bone fragments measuring 6.0 x 6.0 x 1.0 cm in aggregate

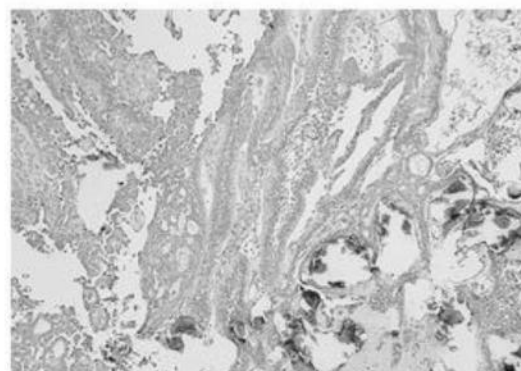


Fig. 11: LPO. The tumor cells are arranged as nodules to elongated structures of atypical odontogenic epithelium with central stellate reticulum (center). A small area of bony trabecular involvement is present (bottom right).

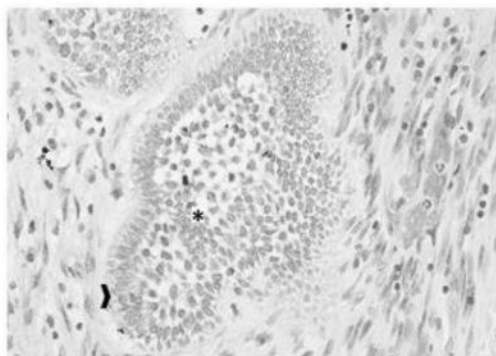


Fig. 12: HPO. Island of odontogenic epithelium with peripheral palisading columnar cells (arrowhead) exhibiting reverse polarization and polyhedral cells at the center (asterisk).

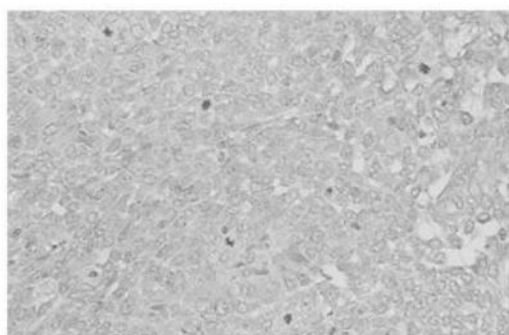


Fig. 13: HPO. Sheet of atypical odontogenic cells with moderate mitosis

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Mycotic Abdominal Aortic Aneurysm in a Patient with Rheumatic Heart Disease: A Case Report*

Abegail Sales Basco, MD¹

ABSTRACT

Rheumatic heart disease is one of the most common acquired heart diseases with valvular heart damage as its hallmark. It is preventable, and the prognosis is good when caught early on. However, serious complications could arise if early detection and prompt intervention are not done. One of its dreaded complication is mycotic abdominal aortic aneurysm, an uncommon sequela that could arise from infective endocarditis. In such cases, surgical intervention is warranted due to its high risk of rupture. The case presented is a 9-year-old female with rheumatic heart disease and infective endocarditis who later developed mycotic abdominal aortic aneurysm. Manifestations were fever, joint pains, left-sided body weakness and abdominal mass. Echocardiography revealed mild aortic insufficiency with vegetations. Abdominal CT scan and CT angiogram showed a mass in the left para-aortic region and a saccular abdominal aneurysm, respectively, which confirmed the diagnosis. Antibiotics and cardiac support were given, and eventually underwent repair of aneurysm with mitral valve replacement. The aim of presenting this report is to highlight one of the rarest complications of rheumatic heart disease and infective endocarditis – mycotic abdominal aortic aneurysm.

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¹Resident, National Children's Hospital, Quezon City

INTRODUCTION

Rheumatic heart disease (RHD) is a complication of a streptococcal throat infection which causes heart valve damage and progressive heart failure if not treated. According to the 2005 summary report by World Health Organization (WHO), the estimated overall burden of RHD was 15.6 million prevalent cases with 282,000 new cases and over 233,000 deaths annually. RHD commonly affects school age children with a prevalence of 5.7 cases per 1000 school children.¹ According to the Philippine Pediatric Society (PPS-ICD 10), there are 5,874 cases of RHD from May 2016 to August 2018.² According to Pediatric Infectious Disease Society of the Philippines (PIDSP), the prevalence of rheumatic heart disease in school children from the year 1981-1990 is 0.6/1000 school-aged children. Complications may arise from rheumatic heart disease if not treated. According to a study done by Okello, complications occurred in 49% of newly diagnosed rheumatic heart disease cases, with heart failure (46.9%) as the most common complication, followed by pulmonary arterial hypertension (32.7%), atrial fibrillation (13.9%), recurrence of acute rheumatic fever (11.4%), infective endocarditis (4.5%) and stroke (1.3%).³ In recent years, the incidence of pediatric stroke has reached up to 8 per 100,000 children per year.⁴ One of the most frequent causes for stroke in the childhood is acquired heart disease. In the National Children's Hospital registry, only 2 cases of stroke secondary to RHD was found among the 758 cases from the year 2006-2016. Infective endocarditis occurs less often in children than in adults and accounts for 1 in 1280 pediatric admissions per year. In the National Children's Hospital registry from the year 2006-2016, 33 had infective endocarditis among 99 cases with rheumatic heart disease. Infective endocarditis is one of the predisposing factors in developing mycotic aneurysm.

Mycotic aortic aneurysm, most commonly known as infected aortic aneurysm, is an aortic aneurysm caused by an infection. The term "mycotic," although a misnomer, was coined by Sir William Osler in his *Gulstonian Lectures* in 1885 where he described a patient with valve vegetations and 4 aortic aneurysms with morphological fungal resemblance. The disease is rare with an estimated incidence of 0.6% of all aortic aneurysm in Western countries. A search of the MEDLINE database found only 41 cases of abdominal aortic aneurysm in

children reported from 1975 to 2008.⁵ No case was documented at National Children's Hospital from the year 2006-2016 except for the patient to be presented who was admitted in 2017. In most cases, aortic aneurysms are atherosclerotic in nature and occur most commonly in the elderly. Most of these aneurysms are of the thoracic aorta, whereas the abdominal aorta is infrequently affected by aneurysms. Although abdominal aortic aneurysm is a rare disease in children, it can be easily diagnosed by imaging studies such as CT angiogram, magnetic resonance angiography and ultrasonography. Aneurysm of the abdominal aorta is associated with high morbidity and mortality. Trauma, connective tissue diseases, granulomatous inflammation and bacterial invasion of the aortic wall accounts for a few of these aneurysms.

The aim of this report is to highlight the rare complication of mycotic abdominal aortic aneurysm which stems from the fatal sequelae of rheumatic heart disease and the importance of early prevention and treatment.

CASE REPORT

This is a case of a 9-year-old Filipino female who came in due to fast breathing. History started 3 months prior to admission when patient had intermittent fever for 3 days with maximum temperature of 41°C. No other accompanying symptoms were reported. Consult was done but diagnosis was undisclosed. She was sent home with Paracetamol which afforded relief of fever. Two months prior to admission, there was recurrence of fever now accompanied with joint pains. Persistence of fever and joint pains prompted consult at a private hospital where Cefixime was given for 7 days but no improvement was noted. About 23 days prior to admission, still with intermittent fever and joint pain, the patient had abdominal pain, fast breathing and pallor. Consult was done at Baler Hospital where he was admitted for 4 days. She was transfused with blood, and unrecalled antibiotics were given. Patient was discharged still with fast breathing. Six days prior to admission, she developed weakness of the left upper and lower extremities. Persistence of weakness on the left side of the body and fast breathing prompted consult at Casiguran District Hospital. He was transferred to our institution for further evaluation.

Review of systems showed weight loss, body malaise and constipation. Patient had no history of trauma or surgery. There was family history of heart disease on maternal side. Claimed to have complete immunization.

At the emergency room, patient was awake, pale-looking and in cardiorespiratory distress. Patient was tachycardic at 136 beats per minute, tachypneic at 64 cycles per minute, afebrile and with oxygen saturation of 90% at room air. When hooked to oxygen support via nasal cannula at 2 liters per minute, oxygen saturation increased to 98%. Patient weighed 14 kg with a z score <-3 (severely underweight), height was 118 cm with a z score of <-2 (wasted). Other pertinent physical findings were pale palpebral conjunctivae, multiple dental caries, palpable cervical lymph nodes, distended neck veins, harsh breath sounds, dynamic precordium, tachycardia with Grade 4/6 murmur, direct tenderness on the right abdominal lower quadrant area, liver edge palpable 3 cm below the right subcostal margin, clubbing of finger nails, and with grade 1 non-pitting edema on the lower

extremities. Neurologic examination showed a patient who was conscious, coherent, with left facial asymmetry and left tongue deviation. Motor examination of the left extremities showed 0/5 or no movement with decrease in bulk and tone. All extremities were equally sensitive to light touch and pressure with normal deep tendon reflex.

Patient was diagnosed as Rheumatic Heart Disease in failure, to consider Stroke. Complete blood count (*Table 1*) showed persistent anemia and leukocytosis with neutrophil predominance. C-reactive protein (12 mg/L) and lactate dehydrogenase (521 U/L) levels were elevated. Bleeding parameters, serum electrolytes, liver enzymes, urinalysis, fecalysis and anti-streptolysin O titer were within normal range. Blood culture on two sites showed no growth. Arterial blood gas done showed respiratory alkalosis with pH 7.552, pCO₂ 51, pO₂ 51, HCO₃ 18.9, base excess -3.5. Electrocardiography (ECG) showed sinus tachycardia with right atrial deviation, biatrial and biventricular enlargement.

Table 1. Complete Blood Count Series

Parameters	Results						
	01-17-17	01-19-17	01-26-17	02-01-17	02-13-17	02-24-17	02-28-17
Hemoglobin	85	97	88	103	99	91	119
Hematocrit	0.28	0.32	0.28	0.32	0.31	0.29	0.36
White Blood Cells	23.3	15.8	10.5	13.1	11.6	11.1	12.4
Segmenters	0.81	0.82	0.93	0.60	0.74	0.63	0.66
Lymphocytes	0.19	0.13	0.05	0.32	0.20	0.25	0.26
Eosinophils	-	-	-	0.02	0.01	0.07	0.04
Monocytes	-	0.05	0.02	0.06	0.05	0.05	0.04
Platelet	300	268	262	393	350	300	314



Figure 1. Chest Radiograph showed markedly enlarged heart with pulmonary congestion and/or pneumonia. Diaphragm and sinuses were intact



Figure 2. Repeat Chest radiograph revealed slight decrease in the transverse diameter of the heart with marked resolution of the pulmonary congestion and/or pneumonia

Chest radiograph (Figure 1) showed markedly enlarged heart with pulmonary congestion and/or pneumonia. Repeat chest radiograph (Figure 2) after 10 days revealed slight decrease in the transverse diameter of the heart with marked resolution of the pulmonary congestion and/or pneumonia.

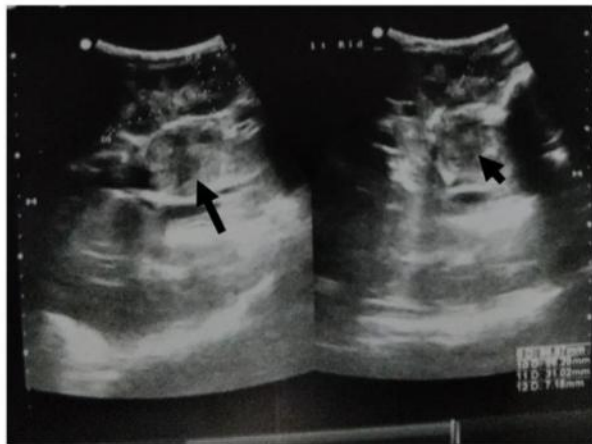


Figure 3 Whole abdominal ultrasound showed 6.5 x 3.3 x 4.3 cm heterogenous isoechoic mass lesion (black arrow) seen in upper abdomen (aortocaval region) with no demonstrable intralésional vascularities to consider large aortocaval lymph node, neoplastic process cannot be ruled out. Normal sonogram of liver, bile ducts, gallbladder, abdominal aorta, pancreas, spleen, kidneys and urinary bladder.

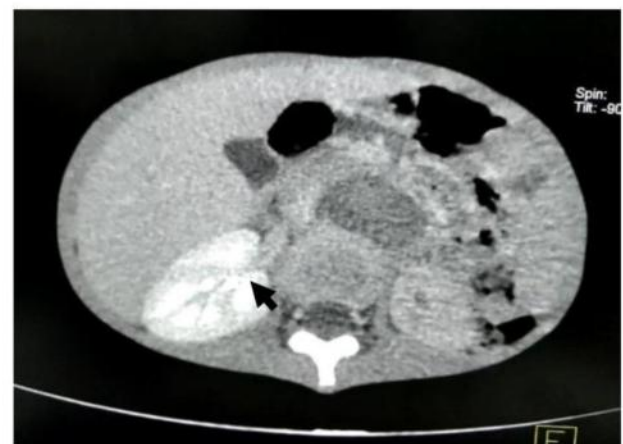


Figure 4. Abdominal CT Scan: oval-shaped mass (black arrow) in the left upper para-aortic region measuring 2.6 x 4.2 x 4.2 cm closely related to the abdominal aorta consistent with a thrombosed abdominal saccular aneurysm probably mycotic seen immediately below the superior mesenteric artery rather than abscess. Hypertrophied right kidney with minimal pelvocaliectasis and a small area of infarct or inflammation. Minimal to moderate hepatomegaly.

Whole abdominal ultrasound (WAB) (Figure 3) was done which showed 6.5 x 3.3 x 4.3 cm heterogenous isoechoic mass lesion in the upper abdomen to consider large aortocaval lymph node; neoplastic process cannot be ruled out. It was also during this time that on physical examination a palpable irregular mass at the epigastric area was noted.

2d echo revealed rheumatic heart disease; thickened mitral valve leaflets; mild aortic insufficiency and trivial pulmonic insufficiency;

good systolic function with ejection fraction of 75% with 3 vegetations at the mitral with in and out motion across the valve, one at the sub-valvar apparatus of the mitral valve and one at the papillary muscle area; with sub valvar membrane noted at the septum below the aortic valve with bridging connection to the papillary mitral stenosis. There was no pericardial effusion. Pulmonary arterial pressure was normal. Abdominal CT scan (Figure 4) showed oval-shaped mass in the left upper para-aortic region measuring 2.6x4.2x4.2cm.

The opacified aorta appears encased by the mass which may represent an abdominal thrombosed saccular aneurysm probably mycotic seen immediately below the superior mesenteric artery. Cranial CT scan showed multiple small areas of slightly hyperdense change with contrast enhancement in the right basal ganglia, right parasylvian area and left splenium corpus callosum consistent with subacute infarcts with disrupted blood brain barrier and lucency perfusion changes. This is secondary to cardio-embolic phenomenon related to rheumatic heart disease. Small area of chronic and ischemic changes. Irregularities of the right midcerebral artery and branches. Minimal ventricular and sulcal dilatation secondary to cerebral atrophy.

CT angiogram of the abdominal aorta done later showed saccular abdominal aneurysm seen just below the level of the superior mesenteric artery extending down the level just before the inferior mesenteric artery, approximately measuring 5.3 x 6.6 x 6.5 cm. There is associated thrombus formation with maximum thickness of 1.6cm and effective luminal diameter of 4.4cm.

Patient was hydrated at BSA 500cc/day. She was given Dobutamine drip at 10mcg/kg/min, Penicillin G (200,000mkd), Gentamicin (7.5 mkd), Captopril (0.5mkd), Furosemide (1 mkdose) and Citicoline 200mg once a day. In the ward, she had 1 episode of melena and later had icterisia. She also continued to be afebrile with occasional abdominal pain radiating to the back and weakness on the left side of the body. Patient was referred to Infectious Service because of mycotic abdominal aneurysm and fluconazole was started. On the 25th hospital day, aspirin was also given for subacute infarcts as seen in the cranial CT scan. Patient completed Gentamicin and Penicillin for 42 days and was transferred to Philippine Heart Center (PHC) for further evaluation of the aortic aneurysm.

At the Philippine Heart Center, patient underwent repair of abdominal aortic aneurysm with mitral valve replacement and was discharge improved. Patient was lost to follow-up and last seen at the PHC OPD on July 2017.

CASE DISCUSSION

Based on the two months history of fever and joint pains accompanied with weight loss, body malaise, fast breathing and physical examination of multiple dental caries, tachycardia, distended neck veins, dynamic precordium, grade 4/6 murmur, hepatomegaly and bilateral non-pitting edema of lower extremities, rheumatic heart disease was highly considered. This was supported by the findings seen on 2d echo. Based on the 2015 Jones criteria, the patient was diagnosed to have RHD in the presence of 1 major (carditis) plus 2 minor (fever, elevated CRP and monoarthralgia) criteria.⁶ The presence of one-week history of sudden left-sided weakness of the body points to a diagnosis of a stroke. Aside from the physical and neurologic examination, this was supported by the findings on Cranial CT scan which showed subacute infarcts secondary to cardio-embolic phenomenon. Multiple risk factors may cause stroke in children. These are arteriopathies, heart conditions, hematologic disorders or inborn error of metabolism. In our case, the presence of rheumatic heart disease and infective endocarditis poses higher risk of developing stroke. History of fever in a rheumatic heart disease with 2d echo findings of vegetations supports the diagnosis of infective endocarditis. According to Duke Criteria, for a diagnosis of endocarditis, 1 major (presence of vegetations in 2d echo) and 3 minor criteria (fever, rheumatic heart disease, vascular phenomenon: aneurysm and intracranial bleed) are needed which were fulfilled in the patient's case.

Rheumatic heart disease is one of the most common and preventable acquired heart diseases with valvular heart damage as the hallmark. It results from an autoimmune inflammatory reaction to throat infection caused by Group A streptococci. It commonly occurs in childhood and can lead to death and life-long disability. The best treatment is to prevent rheumatic fever from occurring. Antibiotic is given to treat the strep infection and patients need to take penicillin possibly for life, to prevent recurrences and lower the risk of heart damage.

Infective endocarditis usually presents with prolonged fever, weight loss, diaphoresis, and myalgias which are secondary to ongoing

bacteremia, valvulitis, embolic and immunological phenomenon. Vegetations may embolize and produce symptoms of ischemia or hemorrhage of the organ involved. In this case report, embolization occurred in the abdominal aorta.

Cardioembolic stroke is diagnosed when sudden focal neurologic signs, maximal at onset, developed in patients with peripheral systemic embolism and recent myocardial infarction or rheumatic mitral stenosis.⁷ There are three basic groups of causes of cardioembolic strokes: (1) cardiac wall and chamber abnormalities (2) valve disorders and (3) arrhythmias. According to Leary & Caplan, among patients with rheumatic mitral valve disease, brain embolism is seen in 7% of patients with mitral insufficiency. Strokes can have a wide range of different clinical manifestations such as sudden hemiparesis, hemisensory loss, confusion, trouble speaking, difficulty understanding, visual loss, diplopia, ataxia, vertigo or even sudden severe headache with no known cause.⁸ There is high incidence of acute midcerebral artery blockage in patients with sudden onset hemispheric strokes. There is limited evidence regarding the efficacy of secondary prevention strategies in childhood stroke however, aspirin is widely used.

In 1885, Osler coined the term mycotic aneurysm to describe infected aneurysm. The term "mycotic" is a misnomer and did not imply fungal etiology. Its classical description is infective aneurysms secondary to rheumatic endocarditis. Most of infected aneurysms were due to infective endocarditis due to streptococcal infection.⁹ Pathology of aortic infection can be explained by several theories. Microemboli may lodge in the vasa vasorum causing occlusion and damage to the aortic wall leading to degeneration and aneurysm formation. It can also be due to direct inoculation into the arterial wall.

According to Sorelius & Summa, for the past 15 years, various combination of the following 4 criteria had been used to diagnose mycotic aortic aneurysm: (1) clinical presentation such as pain, fever, concomitant infection, elderly patient with cardiovascular disease and or immunosuppressive state; (2) laboratory findings of increase inflammatory parameters such as C-reactive protein, leukocytosis and positive culture;

(3) radiological findings on computed tomography or magnetic resonance imaging either saccular, eccentric, multilobular aneurysm, periaortic mass, periaortic gas and rapid aortic expansion, and (4) intraoperative findings. Presence of one of the criteria is not sufficient to make a diagnosis. The patient presented with clinical manifestation of abdominal pain, fever with concomitant infection, leukocytosis, elevated CRP and radiological finding on CT scan of abdominal saccular aneurysm. Once abdominal aneurysm is diagnosed, surgical treatment is required because of the risk of rupture.¹⁰

Abdominal aortic aneurysm is rare in children and various causes have been identified such as connective tissue disorders, arteritis, congenital, iatrogenic, post traumatic and mycotic disorders. Most common causes are infectious-inflammatory, associated with known genetic disease, idiopathic and following trauma, all of which are life-threatening. Treatment of abdominal aortic aneurysm centers around control of hypertension and resection of aneurysm with reconstruction.

Eradication of infection and safe establishment of arterial flow are the goals of management of mycotic aortic aneurysm. The gold standard for treatment of mycotic aortic aneurysm is resection, debridement of infected tissues and graft replacement.¹¹ A minimally invasive option is endovascular therapy. The main goal of surgical treatment is considered after completion of the antibiotics for 4-6 weeks. Often the surrounding tissue is infected with bacteria that it is necessary to do extensive resection. Unfortunately, mortality rate is 40% after open surgical repair.

CONCLUSION

Early diagnosis and prompt treatment can prevent serious life-threatening sequelae of Rheumatic Heart Disease. Diagnostic criteria such as the Duke and Jones criteria with the aid of echocardiography play a major role in the initial diagnosis of these conditions. Prolonged treatment and appropriate prophylaxis are needed to ensure cure and prevent recurrence. Mycotic abdominal aortic aneurysm is a rare complication of infective endocarditis. Early diagnosis is important and

surgical intervention is often needed for effective treatment due to its high incidence of rupture and death. Better understanding of the disease epidemiology, case detection, pathogenic mechanism, primary and secondary prevention may control and reduce incidence of rheumatic heart disease.

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Pachyonychia Congenita Affecting Only The Nails: A Case Report

Marcia Marie S. Marte-Jimenez, MD, DPDS

Krisinda Clare Dim-Jamora, MD, FPDS¹

Maria Jasmin J. Jamora, MD, FPDS²

ABSTRACT

INTRODUCTION: The nails have many functions for daily life including protection of the digits against different kinds of trauma. The nail apparatus is composed of multiple kinds of keratins. Defects in keratin may produce several genodermatoses, which include Pachyonychia congenita. This is a rare genodermatosis that is either autosomal dominant or sporadic. The usual involved keratins are KRT6a, KRT6b, KRT6C, K16 and K17. Keratin defects may manifest on the hair, mucosa, skin and nails. Different presentations of each patient depends on the involved mutated keratins. In rare cases, nail dystrophy may be the only manifestation of the keratin defect.

CASE SUMMARY: A 23 –year-old female presented with a 13-year-history of nail thickening on both fingernails and toenails with no other associated symptoms. She denied oral and skin lesions. She had been unsuccessfully treated with both oral and topical antifungals by several dermatologists. No family members have any similar conditions. She admitted to having hoarseness. On physical examination, nails of both hands and feet marked subungual hyperkeratosis, yellowish to brown- gray discoloration and hypercurvature and rough surface of all 20 nails. The histopathology report revealed marked compact hyperkeratosis, hypergranulosis, papillomatosis and acanthosis. Fungal culture and PAS stain revealed no fungal elements. Patient responded well to nail avulsion and good nail regrowth was noted. She plans treatment of all nails with avulsion.

CONCLUSION: Thorough history, physical examination and histology may help confirm the diagnosis of Pachyonychia congenita, which at times may be mistaken for other nail problems. Treatment is based upon the clinical presentation of the patient. Prognosis for life is good but complications such as infections should be properly addressed.

¹Consultant, Skin and Cancer Foundation, Inc.

²Consultant, Skin and Cancer Foundation, Inc.

INTRODUCTION

The nail protects the distal phalanges and contributes to a variety of motor and sensory functions.

The nail plate is a hard, semi-transparent, slightly convex sheet comprised of tightly packed corneocytes termed onychocytes. It contains abundant "hard" hair-type keratins. Multiple types of keratins are expressed in the nail apparatus and they account for 80% of the dry weight of the nail plate. The pattern of keratin expression within the nail unit explains the involvement of this structure in several genodermatoses that are caused by keratin defects.¹

Pachyonychia congenita (PC) is a rare genodermatosis due to mutation in keratin genes. It is an autosomal dominant disorder caused by mutations in the genes encoding keratins 6a or 16 (PC1) and 6b or 17 (PC2). These keratins are expressed in the nail bed, hair follicle and sebaceous gland as well as palmoplantar, injured and hyperproliferative epidermis.¹

The International PC Research Registry has identified 907 individuals (as of June 2019) worldwide, with genetically confirmed Pachyonychia Congenita and 4 of them was from the Philippines. About 40% of the genetically confirmed Pachyonychia congenita showed mutation in gene encoding Keratin 6a, 32% for K16, 16% for K17, 9% and 3% for K6b and K6c, respectively.²

CASE REPORT

A 23- year old female with a thirteen year history of sudden nail thickening on fingers and toes. No associated skin and oral lesions. Patient reported history of hoarseness for unrecalled number of years. No family members have the same lesions as hers. She consulted few dermatologists in the past and was given oral and topical antifungals with no improvement.

Upon physical examination, there was involvement of the fingernails of both hands (sparing the 5th digit of the left hand S/P nail avulsion) and toenails of both feet; (+) subungual hyperkeratosis, (+) yellowish to brown-gray discoloration; (+) hypercurvature (Figures 1-4).

Fungal culture was requested. Nail avulsion(biopsy) of the 5th digit of the left hand was done. Patient was asked to continue the Amorolfine nail laquer while waiting for the results.

Culture showed no fungal elements. Histopathological report revealed marked compact hyperkeratosis, hypergranulosis, papillomatosis and acanthosis. Within the dermis, there is sparse superficial perivascular lymphocytic infiltrates. No fungal elements are seen on H&E stain.

Patient responded well to nail avulsion and good nail regrowth was noted. She plans treatment of all nails with avulsion.

DISCUSSION

Pachyonychia congenita was a term coined by Jadassohn and Lewandowski in 1906 (Greek: thick nails from birth)³. Pathogenic variants in individuals from at least 494 families has been published to date.² It has equal sex predilection in both male and female.⁴

A proband or the person being reported on, is usually the first person in the family who is affected with Pachyonychia Congenita and usually caused by *de novo* mutation. If the parents of the proband are clinically unaffected, the risk to the siblings of a proband is low, but greater than that of the general population because of the (theoretic, but unlikely) possibility of germline mosaicism. But when the parents of the proband is affected, the risk of the siblings to have the disorder increases to 50%, same risk applies to the offspring of the affected individual.⁴

Keratins form a cytoskeletal intermediate filament network within all epithelial cells. Epithelia in different body regions utilize a range of different keratins. Keratins associated with Pachyonychia Congenita are constitutively expressed in the nail, palmoplantar skin, oral mucosa, and hair. Thus, mutation of the genes encoding these keratins leads to pathology in these major body sites.⁴

Clinical manifestations of Pachyonychia Congenita include hypertrophic nail dystrophy, painful palmoplantar keratoderma and blistering, oral leukokeratosis, pilosebaceous cysts (including

steatocystoma and vellus hair cysts), palmoplantar hyperhydrosis, follicular keratoses on the trunk and extremities, axillary and inguinal cyst formation, excessive production of waxy material in the ear, severe and unexplained ear pain, hoarseness, angular cheilitis and paronychia with pronounced edema.⁴

Pachyonychia congenita tarda (PCT) may represent a delayed form of PC type 1 and underlying cause may also be mutation on Type I Keratin 6a/16 pair. It can be familial or sporadic in nature and the onset of nail changes occurs during the second or third decade of life. Some cases of PCT may also present with palmoplantar keratoderma, leukokeratosis, and cutaneous cysts, while others are only limited to the nails. The reasons behind the late onset of PC in some patients as well as the exclusive involvement of the nails in others are not yet understood.⁵

There can also be variation in clinical severity between mutations in the same gene and even between individuals with the same mutation. Polymorphisms, copy number variation, environmental factors, lifestyle, and patient care are some of the factors for these variations. PC can be considered as a spectrum of phenotypes ranging from very mild to more severe.⁶

The most common presenting sign of Pachyonychia Congenita is plantar pain with plantar keratoderma (including callus with underlying blisters). For patients with genetically confirmed PC, it was reported that 97% presented with the diagnostic triad of toenail thickening, plantar keratoderma, and plantar pain by the age of ten.⁴

The diagnosis of PC is confirmed by identifying the heterozygous pathogenic variant in one of the five genes encoding keratin. It can through serial single gene molecular genetic testing or by multi- gene panel.⁴

Treatment modalities differ from one person to another which depends on the manifestations and more for the symptomatic relief of pain experience by the patient. It varies from mechanical approach to surgical procedures, from topical

therapies to oral medications. Some may even involve lifestyle modifications.⁷ Patients can also be referred to other specialties as needed, hoarseness in a patient with PC should also be referred to an Otolaryngologist for proper assessment and to exclude other laryngeal pathologies.⁸

Prognosis for Pachyonychia Congenita is usually good. Complications like infections should be addressed immediately and continuous care in all aspects should be observed.⁹

CONCLUSION

Pachyonychia Congenita manifestations differ from one affected person to another. It can affect only the nails just like in our case and may look like other nail disorders. Indeed, proper history taking, examination and laboratory tests should be done to for an accurate diagnosis thus right management can be provided to the patient. Genetic tests can if available, can be done for confirmation of mutated involved keratin and genetic counselling may be added for the family education and care.



Figure 1



Figure 2



Figure 3



Figure 4

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A Case of Salivary Duct Carcinoma*

Cecilia Marie M. Holguin, MD¹

Loubomir Cyrus Antonio, MD, FPCS, FPSGS²

ABSTRACT

Salivary Duct Carcinoma (SDC) is a rare type of aggressive cancer that arises from the salivary glands. It is predominantly seen in men and, generally, has a poor prognosis. Other highgrade carcinomas can mimic SDC. About 40-60% of SDC arise in pleomorphic adenomas. Most, if not all, SDCs express androgen receptor by immunohistochemistry. Therapeutically relevant genetic alterations include ERBB2/Her2 amplification PIK3CA and/or HRAS mutations. (Barnes et al.,2005). There are only 200 reportable cases worldwide (Gilbert, 2004). This is a case of a 63- year-old male, who presented with a two-month history of a pre-auricular mass, left associated with pain upon movement of the head from left to right, vice versa. Patient was diagnosed with parotid mass, left, to consider malignancy and underwent total parotidectomy, left with facial nerve sparing. Histopathology results reveal a Salivary Duct Carcinoma. The patient underwent eight cycles of chemotherapy using Cisplatin 50mg and Nimotuzumab 200mg with 32 days of concurrent radiotherapy using a total tumor dose per region 66Gy-post-op bed+(gross neck node level V + 0.5cm CTV margin), PTV 66Gy, No. of Fx: 33, Dose/Fx: 200cGy. At present, the patient is on regular follow up. No definite treatment protocols are published for Salivary Duct Carcinoma due to the lack of reported cases. More cases should be reported so that more definitive future studies will be made regarding this disease entity.

*3rd place, Cancer Awareness Program Case Presentation, Quezon City Medical Society, February 2019

¹3rd year resident, Department of Surgery, Quezon City General Hospital

²Consultant Adviser

INTRODUCTION

Salivary gland tumors are uncommon and only accounts to 2% of all head and neck neoplasms. Out of 2% from the said population, 85% arises from the parotid gland (Brunicardi et.al, 2015). According to the recent list of Cancer facts and figures 2017 and Philippine Cancer facts 2015, salivary duct carcinomas are not among the common cancers seen in both men and women. According to studies, majority of parotid gland mass are benign. Most of the tumors which are malignant in nature came from the minor salivary gland.

Salivary Duct Carcinoma is an aggressive and rare adenocarcinoma which resembles high-grade breast ductal carcinoma. It represents 9% of salivary malignancies. The male to female ratio is at least 4:1. Most patients present after age of 50 years. The parotid is most commonly involved, but submandibular, sublingual, minor salivary gland, maxillary and laryngeal tumors have been reported (Barnes, et.al 2005).

GENERAL OBJECTIVE

To present a case of Salivary Duct Carcinoma in a 60-year old patient.

SPECIFIC OBJECTIVES

1. To review the treatment options for Salivary Duct Carcinoma.
2. To be able to present a possible diagnostic method to diagnose such a neoplasm.
3. To emphasize the importance of multi-disciplinary approach to its management. (Head and Neck Surgery, Surgery Oncology, Pathology, Radiology, Medical Oncology, Radiation Oncology and Rehabilitation)

CASE REPORT

R.M. 63 years old, Male, Roman Catholic, Married, who came in with a chief complaint of a pre-auricular mass on the left side.

History of present illness started three months prior to admission when the patient noticed a firm, palpable, non-movable, non-tender pre-auricular mass approximately 2.0 cm in size on the

left side. This is associated with pain upon moving the neck and not associated with facial asymmetry. The patient sought consult from a private physician, and was advised to undergo fine needle aspiration biopsy (FNAB) which revealed atypical cells of the parotid gland, left. The patient was also advised for CT scan with contrast of the head and neck which revealed 3.4x2.9 cm heterogeneously enhancing mass at left parotid gland. Laboratory tests and imaging were done and the patient was advised to undergo total parotidectomy, left.

The patient's past medical history includes hypertension for 20 years, anaphylactic shock in 1993, and underwent appendectomy in 1997.

The patient's family medical history includes hypertension, colon cancer, basal cell carcinoma and cerebrovascular disease on maternal side.

He is a government employee, 20 pack year smoker, and alcoholic beverage drinker.

On systems review, patient had no weight loss, blurring of vision, hearing loss, difficulty of breathing, chest pain, palpitations, dysuria, bloated sensation, diarrhea, constipation, melena or hematochezia. Pain at the left side of the preauricular area was noted.

Upon admission, patient was conscious, coherent, not in distress; Glasgow Coma Scale Score of 15 (E4V5M6). Vital signs were as follows: blood pressure of 140/100 mmHg, heart rate of 82 beats per minute, respiratory rate of 18 cycles per minute and the temperature is 36.5 degrees. A mass measuring 3.0 cm, movable, firm, non-tender mass at pre-auricular area, left was noted.



Figure 1: Pre-auricular mass, left

Head and Neck CT scan revealed a 3.4 x 2.9cm heterogeneously enhancing mass noted in the left parotid gland with its epicenter in the superficial lobe with signs of extension to the deep lobe with no definite encasement of retromandibular vein (figure 2). No signs of infiltration to the adjacent muscular and soft tissue planes were noted. Sub-centimeter level III lymph node was noted on the left side. The oral and nasopharynx appeared intact. The right lobe of the thyroid was slightly enlarged with a 1.5 cm hypodense nodule. The impression was a heterogeneously enhancing mass in the left parotid gland as described likely from a new growth. Tissue correlation was suggested. Sub-centimeter level III lymph node, left as described. Enlarged right lobe of the thyroid with a hypodense nodule as described.

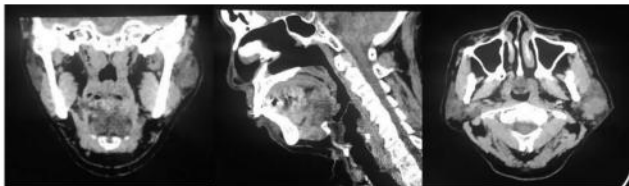


Figure 2: Head and Neck CT Scan without contrast



Figure 3: Head and Neck CT Scan with IV contrast

ADMITTING DIAGNOSIS

Mass, Pre-auricular area, Left, To Consider Malignancy.

COURSE IN THE WARD

Upon admission, patient was awake, alert, not in distress, no difficulty of breathing or shortness of breath with the following vital signs of blood pressure (BP) of 140/100mmHg, heart rate (HR) of 82bpm, respiratory rate (RR) of 18 cpm and with an oxygen saturation of 97%. Patient was placed on a low salt, low fat diet and was hooked to plain NSS 1L to run for 27gtts/min.

On the 1st hospital day, patient underwent Total Parotidectomy, Left with Facial Nerve Sparing. Patient was immediately transferred to Recovery Room and was eventually transferred to his room once his elevated BP normalized. Patient was noted to have asymmetry of the face, more on the left, patient can't close his left eyes, can't close his mouth full, can't elevated his left eyebrows.

On the 2nd hospital day, patient's Glasgow Coma Scale of 15, BP 140/100, HR 75, RR 18, afebrile, noted mildly soaked dressing at surgical site. Patient also complains of pain, inability to eat normally due to difficulty in closing the mouth full, inability to sleep due to difficulty in closing his left eye. Patient was given with pain meds, HTN meds, eye patch applied to left eye, and change of dressing done twice a day. The 3rd and 4th hospital days are unremarkable.

On the 5th hospital day, patient had dry surgical wound, afebrile, can tolerate pain at surgical site, still with asymmetrical face. Patient was referred to Rehabilitation Medicine service for co-management of stimulation of facial nerve. Patient was subsequently discharged and was sent home.

Post-operative, patient had weekly check-up at Rehabilitation Medicine, Quezon City General Hospital (QCGH). The patient underwent eight cycles of adjuvant chemotherapy at QCGH on his second post-operative month and radiotherapy at the University of Santo Tomas Hospital on his third post-operative month. Patient had repeat head and neck CT-scan with IV contrast, complete blood count and liver ultrasound every six months for surveillance.

OPERATIVE FINDINGS

Noted a mass on the parotid area, left measuring approximately 5.0 cm in widest diameter, hard movable adherent to facial nerve extending to the deep lobe, (Figure 4).

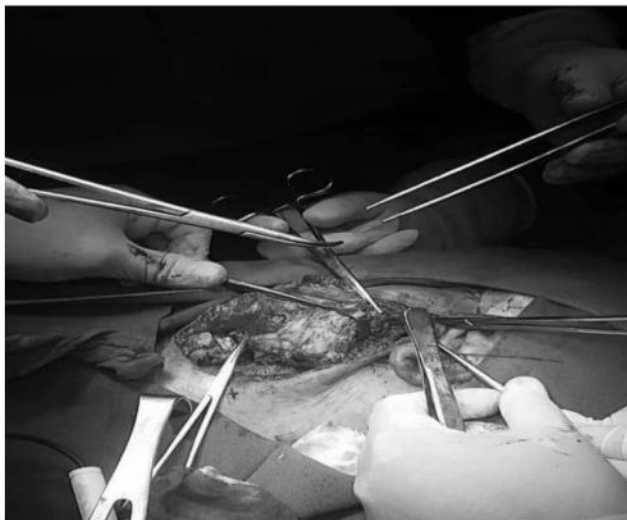


Figure 4: Intraoperative picture, parotid gland, left

POST-OPERATIVE DIAGNOSIS

Salivary Duct Carcinoma, Parotid, Left; s/p Facial Nerve Sparing, Total Parotidectomy, Left (11/27/2017).

HISTOPATHOLOGIC DESCRIPTION

GROSS DESCRIPTION: Specimen received in formalin labeled "parotid gland, left" measures 5 x 4 x 2 cm. It is light tan to gray, irregularly ovoid with firm to rubbery consistency. The surface of the specimen is light tan to yellow and has a slightly granular texture. Cut sections of the specimen reveal a whitish to gray solid parenchyma slightly blending into the adjacent fatty tissue. Specimen received in formalin labeled "deep lobe, parotid" consists of multiple, dark tan tissue fragments with irregular shapes and dull granular surfaces whose measurements range from 1.2 cm to 0.5 cm in diameter. Specimen received in formalin labeled "lymph nodes" measures 4.0 x 2.8 x 1.1 cm. It is gray, irregularly ovoid with firm to rubbery consistency. The surface of the specimen is gray to brown with a granular surface. Cut sections of the specimen reveal a gray to brown solid parenchyma with multiple serrations.

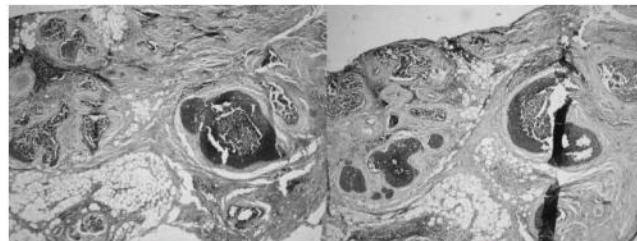


Figure 5. Microscopic image of parotid gland, left

MICROSCOPIC DESCRIPTION

Microsections show cells with hyperchromatic and pleomorphic nuclei with adequate cytoplasm arranged in small cluster and discohesive sheets with an infiltrative pattern. Some show comedonecrosis, (Figure 5).

HER-2-NEU RESULT

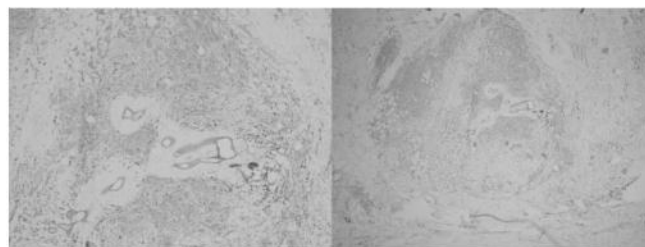


Figure 6. Microscopic image of parotid left with HER-2-NEU

Complete membrane staining with weak to moderate intensity in more than 20% of tumor cells, (Figure 6).

FINAL DIAGNOSIS

Salivary duct carcinoma with a background of sialadenitis; negative for tumor: surgical margins and all six (6/6); lymph nodes examined, lymphoepithelial cyst and focus of Warthin tumor; s/p Facial Nerve Sparing, Total Parotidectomy, Left (11/27/2017).

DISCUSSION

Tumors of the salivary gland are relatively uncommon and represent less than 2% of all the head and neck neoplasms. The major salivary glands are the parotid, submandibular, and

sublingual glands. Minor salivary glands are found throughout the submucosa of the upper aerodigestive tract. The majority of these neoplasms are benign, with the most common histology being pleomorphic adenoma (benign mixed tumor). In contrast, approximately 50% of tumors arising in the submandibular and sublingual glands are malignant. Tumors arising from minor salivary gland tissue carry an even higher risk for malignancy (75%). Salivary gland tumors are usually slow growing and well circumscribed. Patients with a mass and findings of rapid growth, pain, paresthesia, and facial nerve weakness are at increased risk of harboring a malignancy. The facial nerve, which separates the superficial and deep lobes of the parotid, may be directly involved by tumors in 10% to 15% of patients. Additional findings ominous for malignancy include skin invasion and fixation to the mastoid tip. Trismus suggests invasion of the masseter or pterygoid muscles. About 85% of salivary gland neoplasms arise within the parotid gland.

The incidence of metastatic spread to cervical lymphatics is variable and depends on the histology, primary site, and stage of the tumor. Parotid gland malignancies can metastasize to the intra and periglandular nodes. The next echelon of lymphatics for the parotid is the upper jugular nodal chain. Although the risk of lymphatic metastasis is low for most salivary gland malignancies, lesions that are considered high grade or that demonstrate perineural invasion have a higher propensity for regional spread.

Tumors arising in patients of advanced age also tend to have more aggressive behavior. Initial nodal drainage for the submandibular gland is the level 1a and 1b lymph nodes and submental nodes followed by the upper and mid-jugular nodes. Extraglandular extension of tumor and lymph node metastases are adverse prognostic factors for submandibular gland tumors.

Diagnostic imaging is standard for the evaluation of salivary gland tumors. MRI is the most sensitive study to determine soft-tissue extension and involvement of adjacent structures. Unfortunately, imaging studies lack the specificity for differentiating benign and malignant neoplasms.

Diagnosis of salivary gland tumors is frequently aided by the use of FNA. In the hands of an experienced cytologist familiar with salivary gland pathology, FNA can provide an accurate preoperative diagnosis in 70% to 80% of cases. This can help the operative surgeon with treatment planning and patient counseling, but should be viewed in the context that a more extensive procedure may be ultimately required.

The final histopathologic diagnosis is confirmed by surgical excision. Benign and malignant tumors of the salivary glands are divided into epithelial, nonepithelial, and metastatic neoplasms. Benign epithelial tumors include pleomorphic adenoma (80%), monomorphic adenoma, Warthin's tumor, oncocytoma, or sebaceous neoplasm.

Nonepithelial benign lesions include hemangioma, neural sheath tumor, and lipoma. Treatment of benign neoplasms is surgical excision of the affected gland or, in the case of the parotid, excision of the superficial lobe with facial nerve dissection and preservation.

The minimal surgical procedure for neoplasms of the parotid is superficial parotidectomy with preservation of the facial nerve. Enucleation of the tumor mass is not recommended because of the risk of incomplete excision and tumor spillage. Tumor spillage of a pleomorphic adenoma during removal can lead to problematic recurrences.

Salivary duct carcinoma closely resembles ductal carcinoma of the breast, both macroscopically and microscopically, due to its abundance of very firm, fibrous, often ill-defined matrix. Comedo-type necrosis and calcification are seen microscopically, with cystic changes on macroscopic inspection. The majority (80%) of salivary duct carcinoma arises de novo, although in approximately 20 per cent of cases it arises within a pre-existing pleomorphic adenoma.

Survival is better if the tumour proportion is less than 50 per cent, if capsular invasion beyond the mixed tumour extends less than 15 mm, and if cervical nodal disease is absent. A pure, in situ form of salivary duct carcinoma has been described; this

is considered rare and is classified as intraductal carcinoma, but its existence is controversial.

Pure, in situ salivary duct carcinoma has not been recognized as an entity by the WHO classification system. The proportion of intraductal and extraductal growth in reported specimens is variable and has prognostic significance. Although the majority of salivary duct carcinoma behaves in a high-grade fashion, cases which have a predominant intraductal component of greater than 90% and which are minimally invasive (i.e. less than 8.0 mm) are reported to have a good prognosis. The intraductal component may represent the pre-invasive phase of invasive salivary duct carcinoma, which by itself is non-metastasizing and associated with an excellent prognosis. Macroscopically, salivary duct carcinoma is unencapsulated, poorly circumscribed and typically multi-nodular. Comedo-type necrosis, calcification and cystic change may also be seen. Reported tumor sizes range between 1.0 and 10.0 cm.

Microscopically, salivary duct carcinoma arises from the larger intralobular and extralobular ducts, and is characterized by intraductal and infiltrating components similar to the intraductal and infiltrative ductal carcinoma of the breast. Comedo necrosis is evident within the ducts, with 'Roman bridge formation', and evidence of an intraductal cribriform pattern is typically seen. Perineural invasion has been reported in 60 percent of cases, and around 30 percent show lymphovascular invasion.

Most cases of salivary duct carcinoma (SDC) are diagnosed on a hematoxylin and eosin slide preparation. Special stains are at present mainly confirmatory, although some immunohistochemical markers may in future be considered of therapeutic importance.

Three cases were reviewed, and revealed that the patients are male, on their 50s and 60s and presented with a pre-auricular mass. Imaging like CT scan was done and underwent total parotidectomy and neck dissection. Specimens after confirming the diagnosis of SDC were sent for immunohistochemistry. Human epidermal growth factor 2 (HER-2), high molecular weight cytokeratin

(CK-H), CK8/CK18, p63, calponin, the estrogen receptor (ER) and the progesterone receptor (PR) are the requested panel. Chemotherapy and Radiotherapy were done to previous cases and resulted free of cancer for 3 years. In this case, the patient only underwent Her2neu immunohistochemistry, underwent eight cycles of chemotherapy using Cisplatin 50mg and Nimotuzumab 200mg with 32 days of concurrent radiotherapy using a total tumor dose per region 66Gy-post-op bed+(gross neck node level V + 0.5cm CTV margin), PTV 66Gy, No. of Fx: 33, Dose/Fx: 200cGy. After the chemoradiotherapy session, the patient is advised to follow up at regular intervals to monitor for tumor recurrence.

CONCLUSION

Salivary duct carcinoma is one of the most aggressive of the salivary gland carcinomas, and phenotypically resembles high-grade ductal breast carcinoma. The parotid gland is the most common site. Clinically, tumors are typically characterized by a rapidly growing parotid mass with pain, the presence of cervical metastases, and early facial nerve involvement.

Following conventional treatment which comprises of surgery with or without radiotherapy, the local recurrence rate is high, associated with both cervical nodal involvement and distant metastasis, resulting in a poor prognosis.

Treatment needs to be more aggressive, including total surgical removal of the primary site together with a neck dissection. Post-operative radiotherapy should be recommended in all cases. Traditionally, chemotherapy has only been offered for clinically recurrent, disseminated disease. However, evidence suggests that improved disease control could be achieved by employing adjuvant chemotherapy in combination with post-operative radiotherapy.

Advances in immunocytochemistry have identified tyrosine kinase receptors and hormone receptors in salivary duct carcinoma. Certain specific histologic types carry promising immunophenotypic profiles, which should be exploited to identify patients suitable for innovative treatment options, administered within prospective clinical trials.

RECOMMENDATION

This case is recommended to be reported and documented in our hospital, in our country, and in the world since there are only 200 cases reported worldwide and no reportable case in our country. With this, it will increase awareness regarding the said disease, hence better diagnostics and proper attack in the management of the said disease. Immunohistochemical staining for Her2neu will help in the histopathologic diagnosis of such tumors and it also has possible therapeutic implications. Further studies on the presence of Her2neu in these tumors are recommended as there is still no definite criteria to determine the positivity Her2neu in these tumors as of this writing.

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