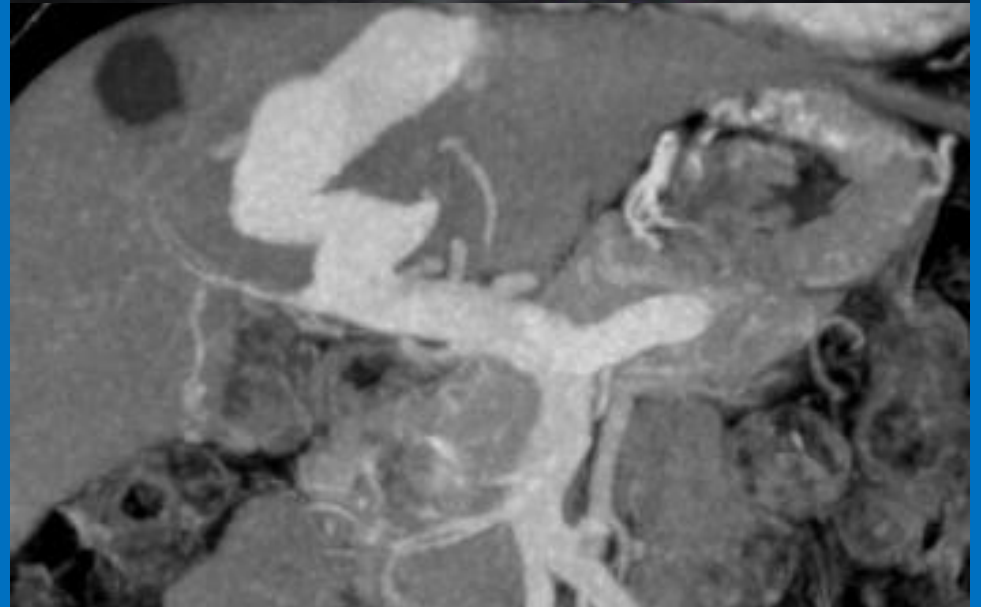
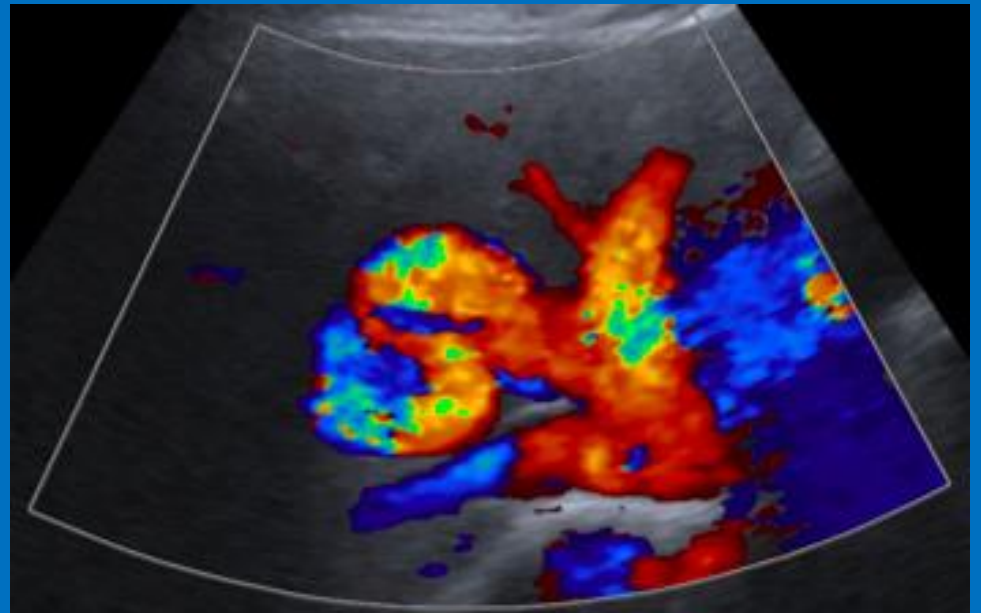




Clinical and Translational  
Research Institute  
The Medical City  
Philippines

# The Medical City Journal

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Cover Photo From: A case report of Spontaneous Intrahepatic Portosystemic Venous Shunt by Nina J. Reinoso and Romelito Jose G. Galsim (*see page 46*).

# THE MEDICAL CITY JOURNAL

The Medical City Journal is the official, peer-reviewed, open-access research publication of The Medical City under the supervision and management of the Clinical and Translational Research Institute (CTRI). TMC Journal caters to all research of the The Medical City network including, but not limited to the following: clinical and biomedical research, case reports, hospital quality improvement research, hospital guidelines/ policy research, novel protocols, systematic literature review and meta-analysis. The aim of TMC Journal is to facilitate dissemination of clinically relevant information to other health practitioners and to the general public.

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## EDITOR'S NOTE

In this second issue of The Medical City Journal, we feature several resident papers as well as a recently published article by members of our very own nursing staff entitled “**Specific stressors relate to nurses' job satisfaction, perceived quality of care, and turnover intention.**”

The study evaluated stressors that affect nurses' job satisfaction and quality of care among 427 of our full-time staff nurses by using a validated tool, the 34-question Nursing Stress Scale. Not surprisingly, the specific stressors identified to decrease job satisfaction were increased workload and the presence of bedside tasks that were non-nursing related. Given the relevance of this article, we asked the primary author some questions regarding their study. (see p. 62 of this journal)

This paper is important because it not only highlights a socially germane issue; it also provides insights regarding the stressors that our nursing workforce faces on a daily basis. In addition, the paper showcases the ability of our staff to produce high quality articles worthy of international publication. The paper is well written, and adds significantly to the nursing literature.

I challenge the rest of the TMC community, and encourage everyone to submit similarly relevant studies, which will impact not only our healthcare here, but elsewhere as well.

**C. Abad**

November 2019



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## Original Article

## Prevalence and Natural History of X-Linked Dystonia Parkinsonism in Koronadal City, South Cotabato

Michael Dorothy Frances Montojo-Tamayo <sup>\*1</sup>, Rachel Suarez-Uy <sup>2</sup>, Donna Mae Lyn Buhat <sup>3</sup>, Jeffrey Tamayo <sup>4</sup>, Roland Dominic Jamora <sup>5</sup><sup>1</sup>The Medical City, Ortigas Avenue, Pasig City; <sup>2</sup>Dr. Arturo P. Pingoy Medical Center, Koronadal City, South Cotabato; <sup>3</sup>St. Anthony Medical Hospital, Marikina City; <sup>4</sup>Roel I Senador Memorial Hospital, South Cotabato; <sup>5</sup>Movement Disorders Center and Section of Neurology, International Institute for Neurosciences, St Luke's Medical Center –Quezon City and Global City, Philippines

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**ABSTRACT:** X-linked dystonia Parkinsonism (XDP) is an adult-onset, progressive, debilitating movement disorder, manifesting predominantly with dystonia in combination with Parkinsonism. It was first reported in 1975 among males in Panay Island. Migrants from Panay Island occupied the region of South Cotabato in Mindanao with its capital Koronadal City. The estimated population of the region is 912,957 as of 2015 and the dominant ethnicity, comprising 51%, are from Panay Island. This paper calls attention to this migration and aimed to identify cases and describe the clinical picture of XDP in Koronadal City. A descriptive study using the screening questionnaire for XDP was used per barangay to look for possible cases. Cases were confirmed through interview and assessment by a movement disorder specialist. Four cases of XDP from Koronadal City were seen. They were all male, presenting with generalized dystonia. The phenomenology of these cases is similar to the 2011 study involving 312 patients. Eleven patients from other municipalities of South Cotabato also came for evaluation and were assessed to have XDP as well. Expansion of this study to involve the entire region of South Cotabato is warranted to provide a more accurate picture of the prevalence and natural history of the disease in the region.

**Keywords:** *DYT3, Koronadal, "Lubag", Panay Island, X-linked dystonia-Parkinsonism, XDP*

## INTRODUCTION

X-linked dystonia Parkinsonism (XDP) commonly known as "Lubag" is an adult-onset, progressive, debilitating movement disorder first reported among Filipino males in Panay Island, Philippines. It presents predominantly with severe, torsion dystonia later combined with or replaced by parkinsonian features. Initially, 93.4% present with focal dystonia while 5.7% present with parkinsonian traits.<sup>1</sup>

The phenomenon, first reported in 1975, described 28 adult males who presented with torsion dystonia with 23 of the subjects from Panay.<sup>2</sup> After 15 years, XDP was characterized as a combination of dystonia and parkinsonism.<sup>3</sup> Twenty-five years after XDP was first reported, more cases were identified and recorded in the registry.<sup>4</sup> As of February 2010, there are 505 cases with 312 survivors.<sup>1</sup> The prevalence rate for the entire Philippines at the time was 0.31 per 100,000 population. For the entire island of Panay, it is 5.74 per 100,000 population with the province of Capiz having the highest prevalence at 23.66 per 100,000, followed by Aklan at 7.72, Iloilo at 1.43, Antique at 0.86, and Guimaras at 0.73.

An XDP Study Group was formed in the 1980s to identify and track cases, and form partnerships with the local government, the Health Department, the Philippine Neurological Association, and academic medical centers. An infrastructure for identification and referral of suspected cases is seen in Capiz, and a system of referral has been developed.<sup>1</sup> Currently, most researches and projects on XDP have focused mainly on Panay Island.

The region of South Cotabato in Mindanao with its capital Koronadal City is populated mainly by migrants from Panay Island (Capiz, Iloilo, Guimaras, and Antique). The Western Visayan provinces of Negros Occidental, Aklan, Antique, Capiz, and Iloilo supplied large numbers of migrants to Mindanao, especially the frontier provinces. Approximately two-thirds of the 311,000 persons born in the western Visayas in 1960 resided in Cotabato. More than half of the persons living in Cotabato who reported birthplaces outside Mindanao were born in the Western Visayas.<sup>5</sup> This dominance of Western Visayan migrants in Cotabato is not solely a postwar phenomenon. This similar pattern of origin among the Koronadal settlers was also noted during the pre-war period. Manuel Quezon created the National Land Settlement Administration (NLSA) to encourage migration to sparsely populated regions in Mindanao. The Koronadal settlement project was among its first with settlers mostly coming from Iloilo, Capiz, Leyte and Cebu.<sup>6</sup>

Currently, the South Cotabato database from the Provincial Planning and Development office, records an estimated population of the region as 912,957 thousand as of 2015. It has ten municipalities and one city, Koronadal. Koronadal has a population of 174,942. The major ethnicities in the entire region are people from Panay Island comprising 469,689 thousand people or 51% of the entire population of South Cotabato. Of the 51%, 1.77% speak Aklanon (native language of Aklan), 1.88% speak Karay-a (also termed old Hiligaynon usually spoken by the people from Antique) and 96.33% speak Hiligaynon with origins from Capiz and Iloilo.<sup>6</sup>



This paper called attention to the migration from Panay Island to the South Cotabato area. It investigated and obtained the clinical picture of XDP cases in this region, particularly in Koronadal City. It intended to identify cases, describe their natural history, and submit them for inclusion in the national registry. It aims for surveillance of XDP cases to be extended to this region with a sizeable Ilonggo population of Panay ancestry.

## METHODOLOGY

### Population

All XDP patients living in Koronadal City who were screened using the X-linked dystonia Parkinsonism screening tool (Appendix 1A) were invited to join the study. Patients were included if they were diagnosed with XDP and living in Koronadal City, South Cotabato, or they were undiagnosed but had symptoms of XDP and were living in Koronadal City. Patients with other known movement disorders were excluded from the study. Informed consent (Appendix 1B) was obtained by the authors from each patient prior to their enrolment. This informed consent was in English and Hiligaynon.

### Methods

This is a descriptive study approved by the Institutional Review Board in a tertiary medical institution.

The study began with a learning session on XDP with 120 midwives and barangay health workers. After the session, they were directed by the city health officer to do case finding and to screen possible cases using the XDP screening tool (Appendix 1A). After obtaining informed consent, participants were subject to a face-to-face structured interview using the data collection form (Appendix 1C) to determine demographic data, family profile, and clinical features of the disease. Specialized neurological examination using the X-linked dystonia Parkinsonism-Movement Disorder Society of the Philippines (XDP-MDSP) rating scale was obtained from the participants.

The screening questionnaire for XDP was developed to identify prevalence of the disease. It is a simple, easy to use, community-based screening questionnaire for the diagnosis of XDP.<sup>7</sup>

The XDP-MDSP is a validated rating scale formulated to rate the severity of Dystonic, Parkinsonian, and non-motor symptoms of patient with XDP and their effects on the patients' activities of daily living (Appendix 1D).<sup>5</sup> The scale has 5 subscales. Most parts of the rating scale are clinician-administered (Parts I, II, IIIA, and V) and the other parts are answered by either the patient and/or his/her caregiver (Parts IIIB and IV).

## Statistical analysis

Data were tabulated as frequencies and percentages. Descriptive statistics such as mean, median, range and standard deviation were tabulated for quantitative variables; proportions were tabulated for qualitative variables.

## RESULTS

The midwives and barangay health workers were able to screen a total of 187 patients. The screening tool for XDP was used and a total of nine participants from Koronadal City were brought in by midwives and barangay health workers. Of these nine patients, four were evaluated to have possible XDP based on age, sex, clinical presentation and positive family history. The other two were more likely Parkinson's disease, while the remaining three were more likely from a structural problem.

Table 1 shows a comparison of the prevalence of XDP among the different provinces of Panay with Koronadal City. With a population of 174, 942 and four cases of XDP, the prevalence in Koronadal City is 2.28 per 100,000. All four participants with XDP were males between 41-50 year of age.

**Table 1.** Prevalence of X-linked dystonia Parkinsonism

POPULATION (per 100,000)	PREVALENCE
Philippines	0.31
Panay	5.74
Capiz	23.66
Aklan	7.72
Iloilo	1.43
Antique	0.86
Guimaras	0.73
<b>Koronadal</b>	<b>2.28</b>

Three families were affected, all having a positive family history, and all coming from the province of Iloilo. The clinical features of these patients (Table 2) show a mean age of onset of 38.25 (range 37-40) years old, and a mean age at initial examination of 40.25 (range 38-45 years old). The mean duration of illness from onset to present is 3.5 years and the mean duration of illness from onset to generalized dystonia was 2.75 (range 2-4) years.

Three of these patients initially presented with cranio-facial symptoms like blepharospasm, facial twitching, and jaw opening. One presented with upper extremity symptoms described as dystonic movements of the right hand. All of these patients presented with generalized dystonia on examination.

**Table 2.** Clinical Features of Patients with XDP in Koronadal City

Variable	
Mean age at onset (years)	38.25 (37-40)
Mean age at initial examination (years)	40.25 (38-45)
Mean duration of illness from onset to present (years)	3.5 (2-5)
Mean duration of illness from onset to generalized dystonia (years)	2.75 (2-4)
Mean duration of illness from onset to predominant Parkinsonism	0
Number of cases initially presenting with parkinsonism	0
Number of cases initially presenting with dystonia	100 %
Craniofacial (%)	75%
Cervical/Shoulder (%)	0
Trunk (%)	0
Upper Extremities (%)	25%
Lower extremities (%)	0
Number of cases with spread (%)	100%
Number of patients with predominantly dystonia	4
Number of patients with predominantly Parkinsonism	0

## DISCUSSION

This is the first research on XDP outside of Panay Island. There are ten municipalities and one city in South Cotabato.<sup>7</sup> In this study, the city of Koronadal was chosen to be investigated first since it is the most populated, and was the first area where migrants from Western Visayas were brought during the pre and post war migration.<sup>5,6</sup> Also, Koronadal City has more access to healthcare and transportation, making it easier to track down cases. Only four cases were seen in Koronadal City. The prevalence rate of 2.28 percent could be an underestimation since the screening per barangay was done by midwives and barangay health workers. It is possible that subtle signs and symptoms of the disease were missed.

The clinical presentation of XDP of the patients in this series all bear similarities to the 312 surviving cases of XDP in a study in 2011.<sup>1</sup> The mean age of onset at 39.67 and mean age at initial examination of 44 years is similar to this study at 38.25 and 40.25 years, respectively. The mean duration of illness from onset to generalized dystonia in the 2011 study is 4 years, while in this paper it is slightly shorter at 2.75. In the 2011 paper, 31% presented with lower extremity complaints followed by craniofacial complaints at 28%, while in our study 3 out of the 4 patients (75%) presented with craniofacial complaints initially. However, having only 4 patients is not enough representation to draw conclusions from. A wider study involving all XDP patients in South Cotabato would provide a better comparison to the 2011 paper.

It is worth mentioning that there were eleven more patients examined for possible XDP but they were living in other municipalities of South Cotabato. Of the 11 patients,

one was female and ten were males. All had a positive family history and all came from the provinces of Capiz, Iloilo, and Aklan. Most presented with dystonia and others already had predominant Parkinsonism. They learned about the evaluation by word of mouth and by recommendation of internists and neurologists in South Cotabato. They were not included in the screening since this study was limited to Koronadal City. Hence, an expansion of this study to the other municipalities of South Cotabato is warranted. It is possible that most patients with XDP decided to settle outside Koronadal City to less populated municipalities due to several factors that can be investigated by future studies. It is of value to offer genetic testing to all of these patients to confirm the disease and to provide genetic counseling. Training of neurologists and internists in the identification and management of XDP, including chemodeneration with Botulinum toxin A is needed.

XDP of Panay Island has spread to different areas due to migration. The cases assessed from Koronadal City and other areas of South Cotabato all bear a similar phenomenology to the cases described with patients in Panay Island. With the knowledge of the migration of people from Panay Island to South Cotabato in Mindanao and the discovery of possible XDP cases through this study, research work should be expanded to this region where the knowledge about the disease is lacking, and help extended to XDP sufferers.

## ACKNOWLEDGEMENT

We would like to thank the mayor of Koronadal City Hon. Peter Miguel MD, the head of the City Health Office Dr. Jean Genevieve Aturdido MD, and the midwives and barangay health workers of Koronadal City for extending their commitment and support in finding cases of XDP in every barangay. This research would not be possible without their help.

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## Original Article

# The Prevalence and Risk Factors of Significant Carotid Stenosis in Patients with Acute Ischemic Stroke in a Tertiary Hospital: A 5-Year Cross-Sectional Study

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**ABSTRACT:** The use of carotid duplex scan is recommended as part of routine screening among patients with acute ischemic stroke. Locally, however, significant stenosis is seldom seen and the rate of carotid intervention is low. This study aimed to: 1) find the prevalence of significant carotid stenosis; 2) identify risk factors for developing significant stenosis; and 3) detect the rate of carotid intervention among patients with acute ischemic stroke. A cross-sectional retrospective chart review was conducted among patients aged 18 years and above who suffered an acute ischemic infarct from January 2013 to August 2018 and were admitted at a Joint Commission International (JCI)-accredited tertiary hospital. Patients who did not undergo a duplex scan during admission were excluded. Data analysis was performed using Stata SE version 13. Quantitative variables were summarized as mean, median, and standard deviation, while qualitative variables as frequency and percentage. Factors associated with significant carotid stenosis were analyzed using logistic regression. The level of significance was set at 5%. Of the 1,607 patients admitted for acute ischemic stroke, 577 (35.9%) underwent a carotid duplex scan. Age ranged from 27-100 years, 56.67% were males, with a median National Institutes of Health Stroke Scale (NIHSS) of 3 and Modified Rankin Scale (MRS) of 0. Of the patients who underwent the duplex scan, 29 (5.0%) had significant carotid stenosis (70%). Only one underwent endarterectomy, and none underwent stenting. The most common risk factors for those with significant stenosis were hypertension (76%), smoking (38%), diabetes (34%) and alcohol (34%). On logistic regression, older age (OR 1.04,  $p=0.005$ ) and higher NIHSS score (OR 1.07,  $p=0.026$ ) were significant factors that increased the chance of having significant carotid stenosis. The prevalence of significant carotid stenosis among patients with acute ischemic stroke was low at 5% with risk factors including hypertension, smoking, and diabetes. In our cohort, the rate of carotid intervention was very low.

**Keywords:** *carotid duplex scan, carotid stenosis, ischemic stroke*

## INTRODUCTION

Significant carotid stenosis (CS) is one potential source of an acute ischemic stroke, apart from the more common causes such as intracranial atherothrombosis, cardioembolic, and small-vessel diseases.<sup>1</sup> Acute stroke patients are worked up for possible etiologies and one of the procedures initially requested is a carotid duplex scan (CDS).<sup>2</sup> Woo et. al noted that the prevalence of atherosclerotic CS in Asian countries varies from one study to the other, ranging from 1.9-12.7% in males and 0.5-6.2% in females. In this study, the overall prevalence of acute ischemic stroke patients that had atherosclerotic CS was low at 1.1%.<sup>3</sup> There is no available local data on the prevalence of risk factors of significant carotid stenosis on acute ischemic stroke patients. There is a need to study the clinical profile of patients with significant CS and evaluate whether there are risk factors that can help identify patients who are at high risk. By doing so, we can refrain from requesting this procedure routinely, lessen hospital costs for these patients, and improve patient care. This study aimed to determine the clinical profile of acute ischemic stroke patients with significant CS. We hypothesized that the clinical profile of patients with significant CS is different from those with insignificant CS.

## METHODOLOGY

### Study design

The investigators conducted a cross-sectional retrospective chart review of patients who suffered an acute ischemic infarct from January 2013 to August 2018 who were admitted at a Joint Commission International (JCI)-accredited tertiary hospital. Review of stenting procedures and endarterectomy for acute ischemic stroke done at the operating room and catheter laboratory of the hospital was also done.

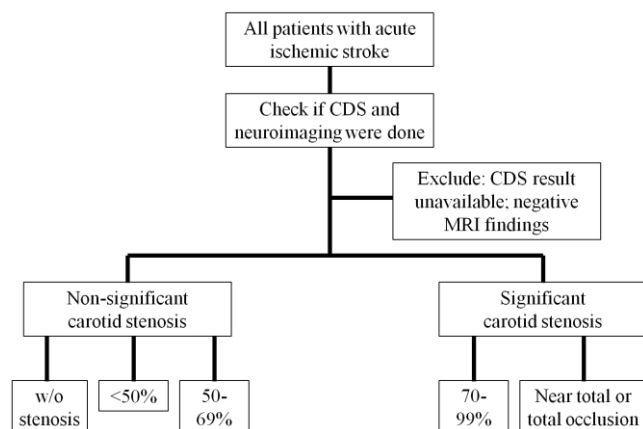
### Participants

Patients aged 18 years and above who were admitted between January 2013 to August 2018 for an acute ischemic stroke and who underwent a CDS and neuroimaging during the same admission were included in this study. The patients should have been referred to or admitted under the care of Neurology service. Patients with inaccessible CDS result and those with negative Magnetic Resonance Imaging (MRI) findings were excluded from the study. Figure 1 shows the study flow diagram.

### Study size

Using Epi Info Version 7, the minimum sample size requirement was set at 380 based on the percent significant

stenosis among patients with acute ischemic stroke =1% with margin of error = 1%.<sup>3</sup>



**Figure 1.** Diagrammatic framework of the study

**Variables**

Acute ischemic infarct was defined as a sudden focal neurologic deficit with imaging-confirmed cerebral infarction.<sup>4</sup> Factors noted to be associated with developing significant carotid stenosis were included. Demographic profile such as age and gender were also taken into account.

To measure stroke severity, the modified National Institutes of Health Stroke Scale (NIHSS) was determined.<sup>5</sup> The individual scores from each item were added up, with a maximum possible score of 42 and a minimum score of 0. To assess the functional capacity of a person prior to the stroke, the Modified Rankin Scale (MRS) was used.<sup>6</sup> It is an ordinal scale with 6 categories ranging from 0 (no symptom) to 5 (complete physical dependence).

Co-morbidities were noted such as diabetes mellitus, hypertension, coronary artery disease, atrial fibrillation, dyslipidemia, and chronic kidney disease (CKD). Diabetes Mellitus was defined as a fasting blood sugar level of 7.0 mmol/L or a 2-hour plasma glucose value of >11.1 mmol/L.<sup>7</sup> Hypertension was defined as having a BP >140/90 mmHg.<sup>8</sup> Coronary artery disease was the narrowing of the coronary arteries due to plaque build-up that was noted on electrocardiogram (ECG) or coronary angiogram.<sup>9</sup> Atrial fibrillation was considered as a supraventricular arrhythmia confirmed by ECG showing an absence of P waves.<sup>10</sup> Dyslipidemia was defined as blood levels of total cholesterol >200 mg/dL.<sup>11</sup> Lastly, CKD was defined as abnormalities of kidney structure or function present for > 3 months with a GFR <60 ml/min.<sup>12</sup> Personal history of smoking, drinking alcoholic beverages, and using illicit drugs were also recorded. In this study, significant carotid stenosis was defined as stenosis of 70% or more of the internal carotid artery as reported on CDS. The presence of carotid stenosis was further classified into one of the following: <50%, 50-69%, 70-99%, and near total or total occlusion.

**Data measurement**

Age, gender, handedness, NIHSS, MRS, past medical history, social history, CDS results, and neuroimaging results were gathered and recorded on a patient data form based on the details found in their medical records.

**Statistical methods**

Data analysis was performed using Stata SE version 13. Quantitative variables were summarized as mean, median, and standard deviation, while qualitative variables as frequency and percentage. Factors associated with significant carotid stenosis were analyzed using logistic regression. The level of significance was set at 5%.

**Ethics and data privacy**

This study underwent ethical and technical review and was approved by the Institutional review board (IRB) of the hospital. Data was kept confidential in accordance with the Data Privacy Act.

**RESULTS**

A total of 1,607 patients were admitted due to an acute ischemic stroke between January 2013 to August 2018. Among these patients, 579 (36%) underwent a CDS. Results of the CDS were available for all patients, but there were two patients who had a negative MRI finding of stroke, hence these two were excluded. A total of 577 patients (35.9%) were included in the study.

Table 1 shows the characteristics of the subjects. Age ranged from 27-100 years with a mean of 60 years. There was a slight male preponderance (56.67%). Median NIHSS score was 3 and median MRS was 0. The most common co-morbidities among those who had a CDS were hypertension and diabetes. More than half of the subjects were non-smokers and non-alcoholic beverage drinkers.

**Table 1:** Demographic characteristics of the subjects

Characteristics (N=577)	Mean ± SD or n (%) or Median (IQR)	
Age in years	59.75 ± 13.54	
Gender		
Male	327 (56.67)	
Female	250 (43.63)	
NIHSS	3 (1 to 4)	
MRS	0 (0 to 1)	
Co-morbidis	Present n (%)	Absent n (%)
DM	252 (43.67)	325 (56.33)
HTN	459 (79.55)	118 (20.45)
CAD	73 (12.65)	504 (87.35)
Atrial Fibrillation	64 (11.09)	513 (88.91)
Dyslipidemia	133 (23.09)	443 (76.91)
CKD	26 (4.51)	551 (95.49)
Stroke	139 (24.09)	438 (75.91)
On Anticoagulant	7 (1.22)	569 (98.78)
On Antiplatelet	87 (15.10)	489 (84.90)
Social History	Yes (%)	No (%)
Smoker	222 (38.47)	355 (61.53)
Alcohol Drinker	238 (41.25)	337 (58.61)
Illicit Drug Use	3 (0.52)	574 (99.48)

Of the patients who underwent CDS, only 29 (5.0%) had significant CS. Characteristics of patients with significant CS included the following: age ranged from 35-96 years; 18 were males and 11 were females; median NIHSS was at 3 and MRS at 0. Table 2 shows the characteristics of the 29 patients with significant stenosis. Of all these patients, only one underwent endarterectomy. No one was managed with stenting. The most common risk factors for those with significant stenosis were hypertension (76%), smoking (40%), and diabetes (36%).

**Table 2:** Demographic characteristics of patients with significant carotid stenosis

Characteristics (N=29)	Present n (%)	Absent n (%)
<b>Co-morbids</b>		
DM	10 (34.48)	19 (65.52)
HTN	22 (75.86)	7 (24.14)
CAD	3 (10.34)	26 (89.66)
Atrial Fibrillation	4 (13.79)	25 (86.21)
Dyslipidemia	5 (17.24)	24 (82.76)
CKD	3 (10.34)	26 (89.66)
Stroke	7 (24.14)	22 (75.86)
On Anticoagulant	1 (3.45)	28 (96.55)
On Antiplatelet	4 (13.79)	25 (86.21)
<b>Social History</b>		
Smoker	11 (37.93)	18 (62.07)
Alcohol Drinker	10 (34.48)	19 (65.52)
Illicit Drug Use	0	29 (100)

Four hundred thirty seven patients (75.74%) had abnormal findings on CDS, while the rest of the 140 patients (24.26%) had a normal result. Patients with abnormal find-

ings had predominantly bilateral ICA stenosis accounting for 77.12%, with majority having <50% stenosis (64.76%) (Table 3).

**Table 3.** Frequency of ICA stenosis based on severity

Degree of ICA stenosis (N=437)	Right ICA (%)	Left ICA (%)	Bilateral ICA (%)
<50%	55 (12.59)	41 (9.38)	283 (64.76)
50-69%	1 (0.23)	0	27 (6.18)
70-99%	1 (0.23)	0	11 (2.52)
Near total occlusion	1 (0.23)	1 (0.23)	7 (1.60)
Total occlusion	0	0	8 (1.83)
<b>Total</b>	<b>58 (13.27)</b>	<b>42 (9.61)</b>	<b>337 (77.12)</b>

Age and NIHSS were both statistically significant factors that increased the chances of having a significant CS. For every increase in age by one year, the odds of having significant carotid stenosis increased by 4.30 (OR=1.0430) (Table 4). Sensitivity analysis showed that 64 years was the cut-off above which there was a tendency to have significant carotid stenosis. For every increase in NIHSS score, the odds of having significant carotid stenosis also increased by 7.14% (OR=1.0714). Sensitivity analysis showed that an NIHSS >4 increased the tendency towards having significant CS. Other factors associated with an increased risk of developing significant stenosis but were not statistically significant included: gender (OR 1.27; p=0.55), MRS (OR 1.28, p=0.18), Atrial Fibrillation (OR 1.30, p=0.64), CKD (OR 2.63; p=0.13), stroke (OR 1.01, p=0.99), and use of anticoagulant (OR 3.23; p=0.286).

**Table 4:** Linear regression analysis for possible predictors of having significant CS

Variable	With significant carotid stenosis (n=29)	w/o significant carotid stenosis (n=548)	Odds ratio (95% CI)	P-value
	Mean ± SD or Frequency (%) or Median (IQR)			
Age (years)	66.8 ± 14.99	59.38 ± 13.37	1.04 (1.01 to 1.07)	<b>0.005</b>
Gender (male)	18 (62.07)	309 (56.39)	1.27 (0.59 to 2.73)	0.548
NIHSS	4 (3 to 6)	3 (1 to 4)	1.07 (1.01 to 1.14)	<b>0.026</b>
MRS	0 (0 to 1)	0 (0 to 1)	1.28 (0.89 to 1.85)	0.181
<b>Co-morbids</b>				
DM	10 (34.48)	242 (44.16)	0.67 (0.30 to 1.46)	0.309
HTN	22 (75.86)	437 (79.74)	0.80 (0.33 to 1.92)	0.614
CAD	3 (10.34)	70 (12.77)	0.78 (0.25 to 2.43)	0.674
Atrial Fibrillation	4 (13.79)	60 (10.95)	1.30 (0.44 to 3.87)	0.635
Dyslipidemia	5 (17.24)	128 (23.36)	0.68 (0.26 to 1.83)	0.448
CKD	3 (10.34)	23 (4.20)	2.63 (0.74 to 9.34)	0.134
Stroke	7 (24.14)	132 (24.09)	1.01 (0.42 to 2.40)	0.995
Anticoagulant	1 (3.45)	6 (1.09)	3.23 (0.38 to 27.7)	0.286
Antiplatelet	4 (13.79)	83 (15.15)	0.90 (0.30 to 2.64)	0.843
<b>Social History</b>				
Smoker	11 (37.93)	211 (38.50)	0.98 (0.45 to 2.11)	0.951
Alcohol Drinker	10 (34.48)	229 (41.79)	0.73 (0.34 to 1.58)	0.430
Illicit Drug Use	0	3 (0.55)	1	-

## DISCUSSION

Stroke etiology differs according to race and ethnicity.<sup>13</sup> In Western countries, cardioembolism or extracranial large arteries are common; while in Asian countries, small-vessel occlusion or intracranial atherosclerosis predominate. Despite this difference, work up for acute ischemic stroke patients remains the same across different populations as we follow the guidelines set by American and European countries.

An inexpensive way to detect CS is through carotid auscultation for bruits. According to Lanzino et.al, it is a sufficient screening test for asymptomatic patients with vascular risk factors. However, for those who are already symptomatic, like patients with stroke, as in this paper, the evaluation for CS cannot be limited to auscultation of the neck because carotid bruits have relatively low sensitivity for detection of moderate or severe CS. This is because bruits are generated when there is turbulence in the flow of blood so they are best heard with mild stenosis. However, when the stenosis becomes severe, bruits tend to disappear because there is already marked restriction of blood flow. Hence, there is a need for carotid imaging such as CDS.<sup>14</sup>

In the UK National Stroke Strategy, part of the basic work up for acute ischemic stroke patients includes CDS within 24 hours of ictus. This is difficult to comply with in a third-world country such as ours because the procedure is relatively expensive; in our institution alone, this costs P6,540. Due to the limited finances of most of our patients and their sole reliance on HMO coverage, only 35.9% of acute ischemic stroke patients were able to undergo the said procedure even if it was requested.

In a study done by Woo, et. al, atherosclerotic carotid stenosis was defined as the presence of a plaque that has > 50% vessel diameter reduction and peak systolic velocity (PSV) >125cm/s or PSV ratio > 2.0. Carotid plaque on the other hand was defined as the presence of plaque that has <50% vessel diameter reduction.<sup>4</sup> In their study comprised of 3030 participants with acute ischemic stroke, atherosclerotic carotid stenosis was noted in 1.1% and carotid plaque in 5.7%. They found that old age, hypertension, and smoking were significant risk factors for developing atherosclerotic carotid stenosis. They also noted that age >80 years, male sex, hypertension, and hyperlipidemia were significant risk factors for developing carotid plaque.<sup>4,15</sup> In this paper, 5.0% of subjects had significant carotid stenosis, a value that is relatively high compared to previous studies, but still low overall. It can be due to the fact that only about one-third of stroke patients were evaluated with CDS. This is likely due to preference of attending neurologists: e.g. he/she chooses the procedures necessary to be done for a certain patient.

Our study also validated the finding that there seems to be a bigger risk of having a significant CS with increasing age. However, none of the known co-morbidities that

pose as risk factors for significant carotid stenosis were significant in the logistic regression analysis in this study.

According to guidelines, patients with ICA stenosis > 70% but not totally occluded would benefit from carotid endarterectomy (CEA) within one week and ideally within 48 hours from ictus.<sup>16,17</sup> In this paper, we note that 21 of those with significant stenosis were candidates for carotid intervention but only one of them underwent the said procedure. This can be due to the fact that the procedure costs approximately P100,000, an amount that most Filipinos cannot afford. Also, this study did not take into account possible surgeries done at other hospitals beyond the current admission at our institution.

## Limitations and recommendations

This is a retrospective review and certain variables could not be changed or manipulated. For example, the decision of clinicians on whether to request for a carotid duplex scan could not be controlled. Future researchers may want to do a prospective study to further control the variables.

This study also did not take into consideration the presence or absence of intracranial or extracranial atherosclerosis found in neuroimaging. This can be a variable that can potentially be significant; a correlation between MR-angiography and/or CT-angiography findings with the degree of carotid stenosis measured by CDS could have been done.

## Implications of the study

Although guidelines recommend that CDS should be part of the initial evaluation for an acute ischemic stroke, the routine use of CDS may not be warranted as the prevalence of significant carotid stenosis appears to be low. Clinicians need to screen stroke patients who have a high risk for developing significant CS and limit doing CDS as part of the initial work up to avoid unnecessary patient expenses.

Even though we were able to obtain CDS results that would have required carotid intervention, the rate of interventional procedures was very low in our institution. Advising patients who are good candidates for surgical intervention should routinely be done to improve patient status.

## Conclusion

The prevalence of significant carotid stenosis is low at 5%. Age and NIHSS were statistically significant factors that increased the chances of having a significant CS. Gender, MRS, atrial fibrillation, CKD, stroke, and use of anti-coagulant were other factors associated with an increased risk of developing a significant stenosis but were not statistically significant. Finally, the rate of carotid intervention was very low.

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## Case Report

# A case report of Spontaneous Intrahepatic Portosystemic Venous Shunt

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**ABSTRACT:** Intrahepatic portosystemic venous shunts are rare vascular anomalies. Only a total of 42 cases have been reported in literature. This is a case of a 56-year old female who had no history of liver disease, trauma or surgery. The patient presented with altered mental status at the emergency room and was subsequently admitted with findings of hyperammonemia. With the utilization of ultrasound with Doppler studies and CT scan, a large intrahepatic portosystemic venous shunt was detected. Surgical correction was immediately employed to avoid further complications. Ultrasonography with Doppler studies plays an important role in diagnosing this condition and guiding treatment options.

**Keywords:** congenital, intrahepatic portosystemic shunt, spontaneous

## INTRODUCTION

Hepatic vascular shunts are classified as: (1) arteriportal shunts, (2) portosystemic shunts, (3) arteriosystemic shunts, (4) systemic-venous shunts and (5) portal to portal shunts.<sup>1</sup> According to Papamichail et al., congenital portosystemic shunts are rare vascular anomalies caused by abnormal development of fetal vasculature.<sup>2</sup> With these shunts, intestinal blood bypasses the liver and reaches the systemic circulation, thus producing symptoms and complications.

Portal to systemic venous shunts are classified as extrahepatic or intrahepatic. Extrahepatic communications are usually seen in the setting of chronic hepatic dysfunction, i.e. cirrhosis with portal hypertension and are commonly through the coronary vein, esophageal varices, or retroperitoneal collaterals. These shunts were first reported by John Abernethy in 1793, and are known as “Abernethy malformation.”<sup>3</sup> Takahashi et al. states that extrahepatic portosystemic shunts have already been greatly researched on and a number of examples are available in literature.<sup>4</sup> On the other hand, intrahepatic communications are located between intrahepatic portal veins and systemic veins.<sup>3</sup> These shunts are rare and were first reported only in 1964 by Raskin et al.<sup>4</sup>

Park et al. presented a classification of intrahepatic portosystemic venous shunts based on the morphological varieties of the shunt vessels in the liver: type I, a single, large tubular vessel of constant diameter that connects the right portal vein to the inferior vena cava; type II, a peripheral shunt, single or multiple communications between peripheral branches of portal vein and hepatic vein in one hepatic segment; type III, aneurysmal communication between the peripheral portal vein and hepatic vein; type IV, multiple, diffuse communications between the peripheral portal vein and hepatic vein, in both liver lobes. Type I is noted to be the most common among the four categories, while type IV is the least common.<sup>1</sup>

According to Naidoo et al., although intrahepatic portosystemic shunts are usually incidental findings, recognition of these anomalies is important due to possible complications such as hepatic encephalopathy, liver cirrhosis, liver failure, pulmonary arterial hypertension and metabolic abnormalities, e.g. hypergalactosemia and hyperammonemia.<sup>5</sup>

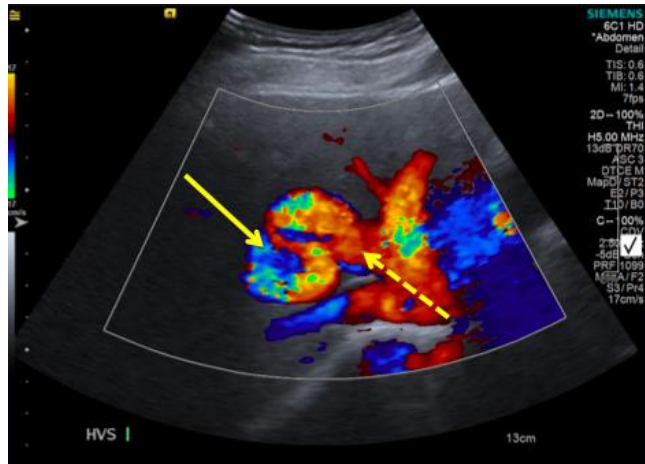
This is a case of type II intrahepatic portosystemic venous shunt, presenting with hepatic encephalopathy and hyperammonemia. The patient was first treated conservatively but subsequently underwent surgical correction. This case report highlights the different imaging modalities that can be utilized to detect and evaluate these rare vascular anomalies.

## CASE REPORT

A 56-year-old female presented at the emergency room with a chief complaint of disorientation. The patient had no history of liver trauma or biopsy, cirrhosis, or abdominal surgery. Laboratory examinations showed increased serum ammonia. A plain cranial computed tomography (CT) scan was done which showed unremarkable results. Initial impression at this time was metabolic encephalopathy, and the patient was subsequently admitted. A contrast-enhanced CT scan of the whole abdomen was requested, which showed a large portosystemic shunt between the right portal vein and middle hepatic vein. No CT evidence of cirrhosis was noted. After conservative treatment with lactulose enema, her ammonia levels normalized and her mental status recovered. Two days after admission, the patient was cleared for discharge and was advised correction of the shunt through surgery or embolization. The patient's final diagnosis was hepatic encephalopathy secondary to a portal vein-hepatic vein shunt.

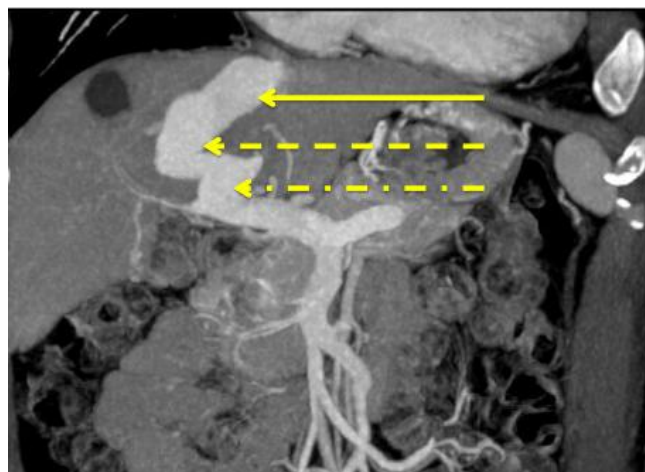
Two weeks after admission, she then consulted with the Center for Liver Disease Management and Transplantation (CLDMT) of The Medical City where further work-up, including a liver Doppler ultrasound (Figure 1), was done. Findings showed a communication between a dilated right

main portal vein and a dilated middle hepatic vein. No evidence of cirrhosis was noted.



**Figure 1.** Ultrasound of the liver with color Doppler studies showing a shunt from the right portal vein (arrow) to the middle hepatic vein (dashed arrow)

Five months after admission, a repeat contrast-enhanced CT scan (Figure 2) of the upper abdomen was then done, which exhibited a stable communication between the right main portal vein and the middle hepatic vein. The patient was advised that the best treatment option was surgical correction of the shunt, but she decided to observe her condition. The patient had no subjective complaints at this time, including altered mental status.



**Figure 2.** Reconstructed coronal portal phase CT image showing a shunt (dashed arrow) between the dilated and tortuous right main portal vein (dot dashed arrow) and dilated middle hepatic vein (arrow)

Seven months after admission, the patient then decided to undergo definitive surgical treatment. She underwent a hepatotomy, dissection and closure of the portovenous-hepatic vein shunt. Intraoperative findings included a dilated

middle hepatic vein with direct communication to the right anterior portal vein. The patient tolerated the procedure well with no reportable events.

On the 6th post-operative day, a repeat liver Doppler ultrasound showed non-visualization of the previously seen communication between the right main portal vein and middle hepatic vein. The patient was subsequently discharged. Follow-up consultation revealed no recurrence of altered mental status, with no late complications following surgery.

## DISCUSSION

According to Takahashi et al., an intrahepatic portosystemic venous shunt (IPSVS) is defined as a communication, measuring more than 1 mm in diameter, between an intrahepatic portal vein and a systemic vein via an anomalous intrahepatic venous channel.<sup>4</sup> Only 42 cases of intrahepatic portosystemic venous shunt have been reported in the English-language literature.<sup>6</sup>

An IPSVS can be classified as either acquired or congenital. Most cases of IPSVS develop in the setting of chronic hepatic dysfunction, such as hepatic cirrhosis, as well as following hepatic surgery or trauma. When a patient presents with an IPSVS without a history of liver disease, trauma or surgery, it is presumed to be congenital or spontaneous in origin.<sup>7</sup> This patient denied any history of liver disease, trauma or surgery that may have predispose her to developing this vascular abnormality. As stated by Torigoe et al., congenital IPSVS is a rare condition with a reported prevalence of 0.0235% in the general adult population.<sup>8</sup>

Embryologically, the development of the hepatic venous system starts by the 5<sup>th</sup> gestational week, with three major paired veins draining into the sinus venosus. These three paired veins are: the vitelline veins, umbilical veins and cardinal veins. The vitelline veins anastomose with each other around the developing duodenum and pass through the septum transversum (primitive liver) to the sinus venosus. A persistent communication between the vitelline veins and the sinus venosus is the presumed basis for intrahepatic portosystemic shunts.<sup>6,9-10</sup>

According to Naidoo et al., IPSVS are typically incidental findings on imaging studies, or on presentation of complications such as hepatic encephalopathy, liver failure, cirrhosis, pulmonary arterial hypertension and metabolic abnormalities such as hypergalactosemia and hyperammonemia.<sup>5</sup> The patient first presented with altered mental status and hyperammonemia. With the help of the CT scan, the intrahepatic shunt was detected. Unlike other congenital diseases, the presence of this anomaly may not be recognized early due to the time it takes to develop hepatic encephalopathy. Patients with congenital IPSVS, whether extrahepatic or intrahepatic, usually develop hepatic encephalopathy during mid adult life, just like in this

patient. Whether these patients develop symptoms depends on the calculated shunt ratio, the sensitivity of the brain to ammonia and the liver function of the patient. The onset of altered mental status in mid adult life may be explained by the fact that the risk for developing hepatic encephalopathy increases with age as the cerebral tolerance for hepatotoxic substances decrease.<sup>4</sup>

To confirm the diagnosis of IPSVS, Doppler sonography, contrast-enhanced CT, MRI and angiography can be used.<sup>11</sup> Gallego et al. states that ultrasound with Doppler studies is the single most important imaging for the diagnosis of IPSVSs.<sup>12</sup> A B mode real-time sonography study usually shows abnormal cystic or tubular, anechoic, serpiginous vascular structures communicating between portal venous structures and the systemic circulation.<sup>5</sup> With the utilization of Doppler ultrasound, the vascular nature of these structures can be confirmed, as well as calculation of blood flow volumes and shunt ratio. Blood flow volume is calculated by multiplying the cross sectional area by the mean velocity. According to Singh et al., shunt ratio is derived by dividing the total blood flow volume in the shunt divided by the blood flow in the portal vein.<sup>13</sup> Low shunt ratios (<30%) have been found to not cause hepatic encephalopathy, even in patient with cirrhosis. Regardless of age, shunt ratios that are greater than 60% should be corrected due to the risk of encephalopathy and liver dysfunction. The patient has a calculated shunt ratio of 70%, which explains her symptoms and risk for complications. CT scan and MRI both help confirm the diagnosis, but their roles have yet to be identified.<sup>9</sup> MRI provides a similar picture with that of CT, with the advantage of the use of non-ionizing radiation, as well as MR venography. Aside from liver Doppler studies, nuclear medicine can also be utilized to calculate the shunt ratio by portal scintigraphy with the administration of submucosal rectal injection of iodine-123 iodoamphetamine.<sup>5</sup> The advantages of liver Doppler studies over these other imaging modalities include: greater availability and accessibility, lower cost and non-invasiveness.

Several factors are considered to establish a treatment plan for patients with IPSVS. These include, type of shunt, location, degree of hepatic function, patient age, symptoms and complications. The therapeutic goal is to cut off the abnormal communication between the portal and systemic circulation, and restore portal flow to the liver. In the pediatric population, it has been concluded that all persisting shunts after the first year of life should be corrected, without waiting for symptoms to develop. On the other hand, asymptomatic adult patients with low flow shunts (<30% shunt ratio) can be observed and monitored with arterial ammonia levels and serial Doppler studies.<sup>2</sup> As stated by Naidoo et al., treatment options include surgical correction, transcatheter embolization or liver transplantation, as a last resort.<sup>5</sup>

## Conclusion

IPSVS are rare vascular abnormalities that may be detected incidentally or on presentation of complications. Several imaging modalities can be used for diagnosis, however, ultrasonography with Doppler studies is the single most important tool due to its availability, accessibility, low cost and non-invasiveness. In addition, the shunt ratio, which is greatly used for guiding treatment options, can be derived using ultrasonography with Doppler studies.

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## Case Report

# Low Dose Thrombolytic Therapy in the Eldest Filipino at 96 years-old

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**ABSTRACT:** Thrombolytic therapy using intravenous tPA (Tissue Plasminogen Activator) or alteplase is the standard treatment in patients presenting within 4.5 hours of ischemic stroke, but elderly patients have mostly been excluded from acute revascularization studies due to hemorrhagic complications. The concern for the hemorrhagic transformation in Asian populations has led to the use of low-dose alteplase (0.6mg/kg) instead of the standard dose at 0.9mg/kg. Shunsaku et al. in 2014 showed feasibility and efficacy of low dose thrombolysis. Stroke risk increases exponentially with increasing age, and there is a low rate of thrombolysis among the extremely old patients (>85 years old) with ischemic stroke. We report a 96 year old Filipino female, with multiple co-morbidities, who had an acute right middle cerebral territory ischemic stroke, with a total National Institutes of Health Stroke Scale (NIHSS) of 19, who received low dose thrombolytic therapy with significant improvement of neurologic status without adverse outcomes. Low-dose alteplase can be a safe and effective thrombolytic strategy in the extreme elderly population.

**Keywords:** Stroke, Thrombolysis, Elderly Acute Ischemic Stroke, Low-Dose Recombinant Tissue Plasminogen Activator, rTPA

## INTRODUCTION

Human nervous tissue is rapidly and irretrievably lost as stroke progresses and therapeutic interventions should be emergently pursued. The typical patient loses 1.9 million neurons each minute in which stroke is untreated.<sup>1</sup> Stroke is one of the leading causes of death and is the leading cause of permanent disability and disability-adjusted loss of independent-life years. Thrombolytics increase the chance of a good outcome by 30%.<sup>2</sup> This treatment can be administered up to 4.5 hours of symptom onset in many patients with ischemic stroke. The Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) concluded that patients < 80 years old are appropriate candidates for thrombolysis.<sup>3</sup>

It is favored to use low-dose alteplase when patients are thought to be at high risk of bleeding such as in older patients, those with decreased renal function, or when endovascular treatment is anticipated.<sup>4</sup> To our knowledge, there are no local published studies of low-dose recombinant tissue plasminogen activator (rt-PA) therapy for patients, ≥ 80 years old with acute ischemic stroke (AIS).

## CASE REPORT

This is a case of a 96 year old female, Filipino, right handed, known hypertensive, with permanent atrial fibrillation (CHADSVASC 6 HASBLED 2), functionally dependent on most activities of daily living, and needing assistance with ambulation. Patient had a chief complaint of sudden onset left sided weakness. Patient was last seen well and asymptomatic at 2 hours 30 minutes prior to consult, when patient was still eating dinner and conversant. Few minutes later, she had sudden onset of slurring of speech, preferential movement of her right extremities, then had decreased sensorium. She was then immediately brought to the tertiary hospital ER at around 2 hours and 45 minutes post

ictus, where the rapid response team called the Brain Attack Team was activated. Neurologic exam revealed the patient was drowsy, severely dysarthric, with left homonymous hemianopsia by visual threat, pupils 3mm equally brisk and reactive to light, preferential gaze to the right, left central facial palsy, hemiplegic on left upper and lower extremities, and with Babinski on the left. The total National Institutes of Health Stroke Scale (NIHSS) was 19. An emergency cranial CT scan done at around 3 hours and 30 minutes post ictus showed acute infarct on the right middle cerebral territory. Thrombolysis was then initiated after consent was given, at a low dose of 0.6mg/kg dose, compared to the standard 0.9mg/kg, to reduce possible hemorrhagic complications in this age group. During the hospital course, patient showed improvement of neurologic status. Her sensorium improved. She still had mild dysarthria with a midline gaze. Motor examination showed improved strength of the left upper and lower extremities as patient was able to raise extremities against gravity. Three months post thrombolysis, and with adequate neurorehabilitation, patient had minimal residual on her left side and her motor strength was back to baseline.

## DISCUSSION

In the extreme elderly population, thrombolysis is considered an option but poses several risks as they are thought to have higher propensity to have hemorrhagic complications.<sup>5</sup> In one study in Italy done by Toni, D et al., the efficacy and safety of the use of intravenous thrombolysis using the standard dose 0.9mg/kg in patients aged >80 years was evaluated and compared with that in younger individuals to determine the incidence of good functional outcomes three months after the stroke.<sup>6</sup> Good outcomes were defined as those with modified Rankin Scale (mRS) scores of 0–2, and poor outcomes included death or dependency (mRS scores of 3–5). According to the study, no

difference in the incidence of intracerebral hemorrhage was observed between the groups. Additionally, the positive and negative outcomes of the thrombolytic treatment were not statistically different between the two cohorts after three months. Those aged >80 years had a statistically higher mortality rate than the younger group. The NIHSS score predicted mortality and poor outcomes in the older group. However, the final outcome of this study suggested that thrombolytic therapy should also be available to elderly patients, i.e. those aged >80 years.

Although the risk of stroke increases with age, some physicians remain cautious about administering thrombolytic therapy to very elderly patients who experience an acute ischemic stroke. Mateen et al. were the first to examine alteplase treatment in patients aged >90 years, using retrospective data from four medical centers between 1999 and 2008.<sup>7</sup> The authors examined clinical neurological symptoms, complications, and outcomes of patients with acute ischemic stroke after alteplase treatment. The study included eleven women, with ages ranging from 90–101 years. The range of time to alteplase treatment was 90–180 minutes. The patients had a range of NIHSS scores of 5–28. Nearly all patients were mobile before the stroke (median mRS score, 1; median Barthel Index score, 95); only one patient had minimal movement restrictions. After 30 days of observation, two patients had a positive outcome, and two others had slight disabilities. The majority of patients died or had severe mobility problems, and three had asymptomatic cerebral hemorrhages. Thus, alteplase treatment did not appear to improve outcomes. However, better results were obtained with alteplase treatment in patients with acute ischemic stroke aged >90 years in another recently published study by Sandercock et al.<sup>8</sup> In this study, 111 patients with acute ischemic stroke aged >90 years were treated with rt-PA. The majority of patients aged >90 years benefited from treatment with rt-PA within the 3-hour treatment time frame in this study.

A meta-analysis done by van Asch CJ et al. showed that the East Asian population have had higher prevalence of hemorrhage compared to Western population.<sup>9</sup> The concern for the hemorrhagic transformation in Asian populations has led to use of low-dose alteplase (0.6mg/kg) instead of the standard dose of thrombolysis at 0.9mg/kg alteplase.<sup>4</sup> A study done by Takanayagi et al, in Japan evaluated the safety and effectiveness of low-dose recombinant tissue plasminogen activator (0.6 mg/kg) therapy for elderly acute ischemic stroke patients ( $\geq 80$  years old) in the pre-endovascular era.<sup>10</sup> This study showed that the incidence of symptomatic intracerebral hemorrhage was not significantly different between the younger (4.3%) and older (0%) groups ( $p = 0.61$ ). The recanalization rate of the occluded artery was also similar between the younger (54%) and older (50%) groups ( $p = 0.78$ ). The rate of a low mRS score (e.g. 0–2) three months after stroke was significantly higher in the younger (44.3%) than in the older group (11.8%) ( $p = 0.013$ ). Low-dose rtPA therapy appears

to be as safe and feasible for adult  $\geq 80$  years old as it is for younger people. Three months following tPA therapy, approximately 30% of patients were neurologically normal or near normal; 30% had mild to moderate neurological deficits; 20% had moderate to severe neurological deficits; and 20% died.<sup>2</sup>

This case of a 96-year-old female Filipino given thrombolysis for acute ischemic stroke shows that the alternative low-dose alteplase strategy has comparable effectiveness and safety to the standard. There was no further deterioration of functional status. There was no significant adverse effect like bleeding during infusion. It could be a practical option at least for ischemic stroke patients of East Asian ancestry who are expected to have a higher risk of cerebral hemorrhages. Despite the anticipated worse outcomes among the older patients compared to the younger patients, an association between thrombolysis and improved outcomes can be observed in the very elderly. This case suggests that age should not be an exclusion criterion for alteplase treatment for acute ischemic stroke.

### Conclusion

Elderly patients have mostly been excluded from acute revascularization studies due to higher hemorrhagic complications.<sup>5</sup> In general, older patients with stroke have worse outcomes compared to the younger population.<sup>11</sup> While thrombolysis clearly shows a benefit in fit and independent older patients who meet the criteria to participate in clinical trials, many elderly patients have significant physical and cognitive co-morbidities, and the risk/benefit ratio for thrombolysis is less well defined. In our opinion, however, even small benefits, i.e. regaining the ability to speak or swallow, improving mobility, can make a big difference in quality of life in this age group.

This 96-year-old Filipino female who was successfully treated with a low dose thrombolytic for ischemic stroke is the first reported case in the Philippines in this age group. Alteplase therapy should not be categorically denied to elderly patients with acute ischemic stroke, based solely on patient age. Because the threshold of 80 years is arbitrary for thrombolysis, physicians should weigh the risks and benefits of intravenous alteplase to treat acute ischemic stroke in elderly patients on an individual basis.

This case report is limited only to the patient's hospitalization. The functional status within six months post thrombolysis could give a more sufficient assessment of the patient's clinical recovery after stroke.

### ACKNOWLEDGEMENT

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## Case Report

# Unlucky Combination: A Report on Two Cases of Herlyn-Werner-Wunderlich Syndrome

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**ABSTRACT:** Herlyn-Werner-Wunderlich (HWW) syndrome, currently known as Obstructed Hemivagina and Ipsilateral Renal Agenesis (OHVIRA), is a rare congenital Mullerian abnormality defined by a triad of didelphic uterus, obstructed hemivagina, and ipsilateral renal agenesis. It affects approximately 0.1-3.8% of women worldwide. This paper discusses two cases of HWW syndrome managed in a private tertiary hospital highlighting the spectrum of signs and symptoms of the disease. It is hoped that this study will inform practitioners and patients about the various presentations and the management of OHVIRA.

**Keywords:** *Herlyn-Werner-Wunderlich syndrome; ipsilateral renal agenesis; Mullerian duct anomalies; obstructed hemivagina; uterine didelphys*

## INTRODUCTION

Congenital Mullerian duct fusion abnormalities are conditions that affect the female reproductive system, specifically the uterus, cervix, fallopian tubes and superior aspect of the vagina. Mullerian anomalies affect 0.1% - 3.5% of females based on retrospective and observational studies.<sup>1</sup> The most common abnormality is a bicornuate uterus comprising 37% of all reported uterine anomalies.<sup>2</sup>

The Herlyn-Werner-Wunderlich (HWW) syndrome is a rare combination of a didelphic uterus, obstructed hemivagina, and ipsilateral renal agenesis. There are no studies mentioning the prevalence of HWW syndrome in the Philippines. However, review of Philippine literature revealed nine reported cases of HWW syndrome.<sup>3,4</sup> In our institution, there has only been one reported case.<sup>5</sup> The incidence found in international literature is 1 in 2000 to 1 in 28,000.<sup>6</sup> The patients with this rare condition usually present with menstrual problems, (amenorrhea, severe dysmenorrhea or intermenstrual spotting) and a palpable mass in the vagina due to accumulation of blood, mucus, or rarely, pus.<sup>7,8</sup> Delay in its diagnosis and management is inevitable due to its rarity; however, the complications can be devastating. The patients with this condition can suffer from endometriosis, ovarian endometrioma, upper genital tract infection, pelvic adhesions, ectopic pregnancy, recurrent pregnancy loss, and infertility.<sup>9</sup> This paper describes two patients with HWW syndrome with different characteristics and management. The first case shows the ideal approach to young patients with Mullerian abnormalities. The second case describes a patient who had several opportunities for early diagnosis. Despite treatment, this patient still showed the long-term complications of HWW syndrome. This study aimed to increase awareness regarding Mullerian anomalies, discuss the ideal diagnostic tools and management for HWW syndrome, and promote early diagnosis and treatment to avoid complications.

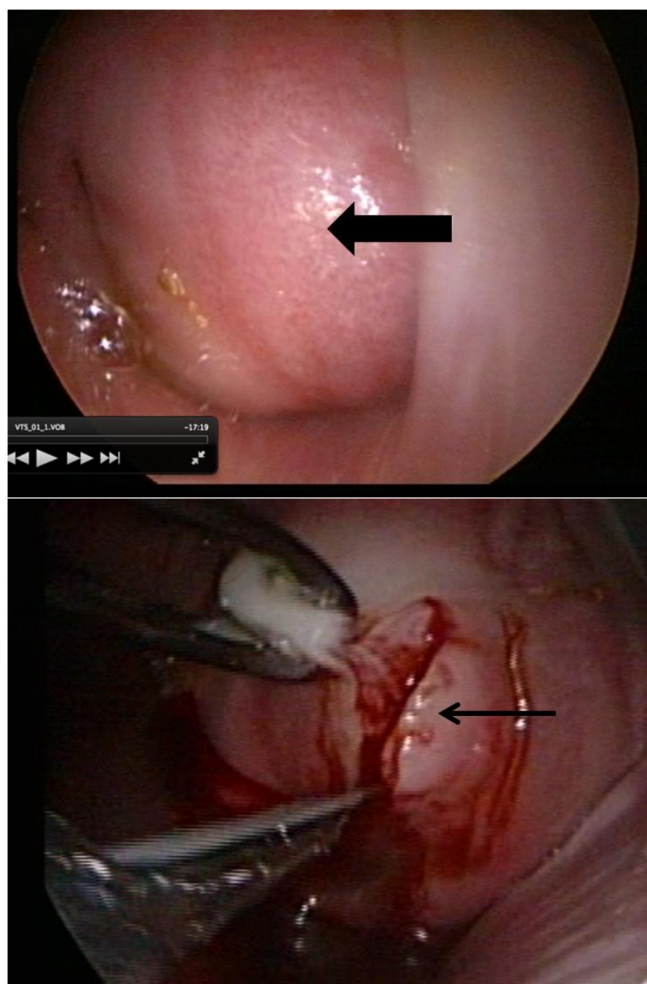
## CASE REPORT

### Case 1

An 18-year old nulligravid with history of sexual contact presented with left lower quadrant pain. The patient has been regularly menstruating since she was 13 years old, lasting for four to five days, consuming four pads per day, fully soaked, with occasional dysmenorrhea. Three months prior to admission, the patient noted sudden onset of left lower quadrant pain not associated with menstruation but with intermenstrual bleeding. Pregnancy test was negative. Increasing severity of the pain prompted consult with an obstetrician-gynecologist. On physical examination, she had normal external genitalia. Speculum exam revealed a 2x2 cm bulge on the superior third of the left lateral vaginal wall with a pink, smooth cervix without erosions and polyps. Internal examination revealed a 2 x 2 cm, slightly tender, movable mass at the superior third of the left lateral vaginal wall. The cervix was firm, long, and closed, without cervical motion tenderness. The uterus was not enlarged and nontender, but there was fullness in the left adnexa with minimal tenderness on deep palpation. There was no right adnexal mass or tenderness. A 2D transvaginal ultrasound was requested which showed uterine didelphys with hematocolpos in the left hemiuterus. The left cervix was dilated to 5.80 x 3.83 x 5.19 cm, fluid-filled, with heterogenous echoes approximately 14.59 ml. There was a left adnexal mass measuring 4.17 x 1.90 x 3.31 cm suggestive of pyosalpinx or hematosalpinx. At the upper third of the vagina, there was an echogenic band 1.37 cm away from the cervix measuring 0.3 cm, a longitudinal vaginal septum confirmed by 3D ultrasound. She was referred to a reproductive endocrinology and infertility specialist who requested a kidney and urinary bladder ultrasound which revealed an absent left kidney and normal sized right kidney. Renal function was normal. Resection of the longitudinal vaginal septum followed by diagnostic hysteroscopy was done (Figure 1). Intraoperative findings revealed 50 ml of chocolate-like fluid drained from the left upper vagina.



No hematometra was noted in the left hemi-uterus. Postoperative course was unremarkable. On follow-up one week after the surgery, there was resolution of the left lower quadrant pain and intermenstrual bleeding.



**Figure 1.** Intraoperative images showing the longitudinal vaginal septum (thick arrow) and resection of the septum (thin arrow).

## Case 2

A 37-year old nulligravid with history of sexual contact and right kidney agenesis since childhood, presented with abnormal uterine bleeding. At the time of diagnosis of kidney agenesis, no workup for gynecologic abnormality was done. Renal biopsy of the left kidney showed focal segmental glomerulosclerosis. She was initially treated with prednisone but she eventually developed end stage renal disease and was started on dialysis six years ago. The patient had been suffering from severe dysmenorrhea and irregular menstruation since 15 years old. Her menses occur at three to six-month intervals, lasting for four to nine days, consuming six pads per day, moderately soaked. She denied other symptoms. At 22 years old, the patient consulted a gynecologist and was diagnosed with an ovarian cyst. She underwent unilateral oophorectomy. After

one year, she transferred to another gynecologist due to the persistence of symptoms. A transvaginal ultrasound was done which showed didelphic uterus and an obstructed right hemivagina. The patient allegedly underwent hysteroscopy with removal of the obstruction. There was resolution of the dysmenorrhea but irregular menstruation persisted. No medical management was offered to the patient. In the interim, there was occasional mild dysmenorrhea.

Six years prior to admission, she was diagnosed with breast cancer, left, stage IIB. She underwent lumpectomy, 28 cycles and five boosters of radiotherapy, and Tamoxifen therapy for four years.

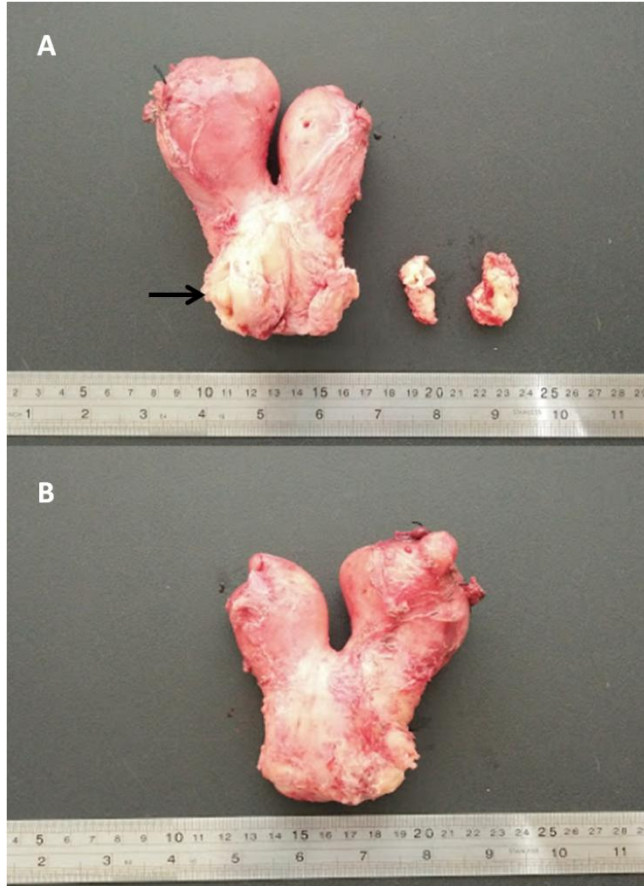
On presentation and upon physical examination, she had normal external genitalia. Speculum exam showed a pink and smooth cervix with minimal non foul-smelling brownish discharge, without erosions or polyps. Internal exam revealed a long, firm, closed cervix, without motion tenderness. Both hemiuteri were enlarged to 12 weeks size, nontender with no noted adnexal mass or tenderness. Rectovaginal exam showed tight sphincteric tone, intact rectal vault and rectovaginal septum. Transvaginal ultrasound was done which showed uterine didelphys, single cervix with two cervical canals and two vaginas, the right hemivagina obstructed in the middle third with a septum. No hematometra or hematocolpos was noted.

Upon exploration, both hemiuteri were densely adherent to the sigmoid colon and anterior abdominal wall. The right ovary and fallopian tube were densely adherent to the pelvic sidewalls. The left ovary was cystically enlarged and multiloculated measuring 5.5 x 5.0 x 2.0 cm, exuding clear fluid upon rupture. The right endometrial cavity exuded chocolate brown fluid upon opening, with note of smooth endometrium. The right cervix appeared to be obliterated. The patient underwent total abdominal hysterectomy with bilateral salpingoophorectomy and adhesiolysis. Histopathology revealed uterine didelphys, leiomyoma in the right hemiuteri, secretory endometrium, endometriosis in the right ovary and fallopian tube, and endometriotic cyst, left ovary (Figure 2). The patient tolerated the procedure well and no complications were noted. Postoperatively, there were no immediate complications but on follow-up with patient one year after surgery, there was noted postmenopausal symptoms such as vaginal dryness and hot flashes. The patient was initially offered menopausal hormone therapy but was lost to follow-up.

## DISCUSSION

Herlyn-Werner-Wunderlich syndrome was first described by Purslow in 1922 and was first named as a syndrome of obstructed hemivagina, uterus didelphys, and ipsilateral renal agenesis in 1971.<sup>11,12</sup> The development of the mullerian and renal system occurs side by side at the same time. The possible etiology of the HWW syndrome is thought to be due to a disruption in the development of the caudal portion of one mesonephric duct with secondary

involvement of the ipsilateral Mullerian duct. This affects the normal ureteric budding and kidney differentiation in one side leading to renal agenesis and abnormal location of the ipsilateral Mullerian duct. Due to this, the abnormal Mullerian duct fails to combine properly with its counterpart leading to a double uterus and an obstructed cervical or vaginal canal.<sup>13,14</sup>



**Figure 2.** Uterus didelphys (A) anterior view (B) posterior view with leiomyomata in the right hemiuterus (arrow).

The most widely used Mullerian anomaly classification system is that of the American Society for Reproductive Medicine (ASRM) (Table 1).<sup>1</sup> Patients with didelphic uterus or those with complete or partial duplication of the vagina, cervix, and uterus are classified under Class III. There are several classification schemes for Mullerian anomalies such as the ESHRE/ESGE (European Society of Human Reproduction and Embryology) but the ASRM classification is the most widely accepted since it organizes anomalies according to the major uterine anatomic defect allowing standardized reporting of cases. However, one of its limitations is that some complex conditions such as HWW syndrome cannot be included in the classification system because of the lack of categories for cervico-vaginal and genitourinary anomalies.<sup>1</sup>

**Table 1.** AFS/ASRM Classification of Congenital Anomalies of the Female Genital Tract.

Classification	Uterine anomaly	Associated Anomalies
Class I	Hypoplasia and agenesis	(a) Vaginal (b) cervical (c) fundal (d) tubal
Class II	Unicornuate	(a) communicating (b) noncommunicating (c) no cavity (d) no horn
Class III	Didelphys	
Class IV	Bicornuate	(a) partial (b) complete
Class V	Septate	(a) partial (b) complete
Class VI	Arcuate	
Class VII	Diethylstilbesterol drug-related	

Patients who have HWW syndrome are usually asymptomatic until menarche. Most commonly, they present with severe and progressive dysmenorrhea, as well as irregular menstruation and intermenstrual spotting. Most patients who have these symptoms are those with microperforation or a small communication between the obstructed and non-obstructed side, signifying accumulation of menstrual blood in the obstructed hemiuterus or hemicervix then gradual drainage through the perforation.<sup>7,8</sup> However, these symptoms may be misdiagnosed as pelvic endometriosis, delaying important workup such as kidney and urinary bladder ultrasound. These patients may also have fertility problems such as spontaneous abortion in 40% of cases, most probably due to the uterine malformation.<sup>14</sup> On physical examination, a tender suprapubic or abdominal mass may be felt and this may be caused by a hematometra. On the other hand, a hematocolpos may present as a paravaginal or paracervical cystic mass, as seen in the first case. Both cases presented with dysmenorrhea but the second patient presented with more severe symptoms including irregular menstruation. Ironically, it was the second patient who was diagnosed late, probably because the first patient presented with acute symptoms, prompting gynecologic consult immediately.

Delay or misdiagnosis of Mullerian abnormalities can have serious consequences in the upper genital tract such as endometriosis, hematosalpinx, and pelvic adhesions.<sup>8</sup> Possible pathogenesis of these conditions is retrograde menstruation caused by the obstruction. Rarely, infection in the lower vaginal tract may ascend to the upper genital tract causing pyocolpos or pyosalpinx.<sup>6</sup>

The gold standard for diagnosing Mullerian anomalies is the combination of hysterosalpingogram (HSG) and laparoscopy.<sup>19</sup> The imaging of choice in Mullerian anomalies is an MRI (especially T2-weighted imaging) due to its accuracy and better resolution in delineating soft tissue such as the uterus and vagina.<sup>16</sup> However, due to multiple reasons such as availability, accessibility, lower radiation exposure, and cost, ultrasonography is usually done prior to other diagnostic tests. Three-dimensional ultrasound and MRI were found to have a high degree of concordance, and 3D ultrasound was also found to be as accurate as hysteroscopy and

laparoscopy.<sup>17,18</sup> Hence, it is recommended to use a 2D-Ultrasound as screening test and a 3D-ultrasound to serve as a definitive diagnostic test.<sup>1</sup>

Surgical and medical management for HWW syndrome aim to provide symptomatic relief, prevent complications, and maximize the fertility of a patient.<sup>1</sup> For patients with symptomatic obstructed hemivagina, resection of the vaginal septum with marsupialization is the procedure of choice rather than simple incision and drainage because the former is associated with less infection and re-occlusion.<sup>6,7</sup> Simultaneous laparoscopy is not routine for cases of HWW syndrome unless a hematosalpinx or ovarian endometrioma are found on imaging.<sup>6</sup> After surgery, the next step is to suppress menstruation using various medications such as combined oral contraceptive pills, progesterone or GnRH analogs to prevent re-accumulation of menstrual blood.<sup>6</sup>

The incidence of breast cancer in patients with Mullerian anomalies is unknown and no case has been reported in the Philippines. In one foreign study, only two cases of patients with uterine didelphys and breast cancer who underwent tamoxifen therapy were mentioned.<sup>20</sup> Both patients eventually developed endometrial cancer.

The importance of having a high index of suspicion for Mullerian anomalies in the presence of renal abnormalities cannot be overly emphasized. Early intervention is pertinent in order to prevent complications and enhance a patient's chances of reproduction. Despite having a higher rate of spontaneous abortion, the live birth rate of patients with HWW syndrome can be as high as 91% if obstruction is treated.<sup>21</sup> A referral to a nephrologist is also prudent for monitoring of the remaining kidney function. A multidisciplinary team composed of an obstetrician-gynecologist, radiologist, psychologist, nephrologist, and fertility specialist is definitely needed in dealing with patients with HWW syndrome.

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## Feature Article

# Paving the Way Forward: The Medical City Antimicrobial Stewardship Program

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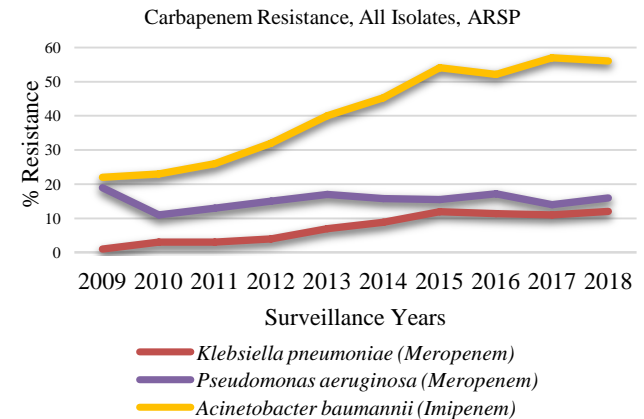
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## Background

The discovery of penicillin in 1928 by Sir Alexander Fleming revolutionized the way physicians treat infections. During his Nobel Lecture in 1945, however, Fleming warned: “The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”<sup>1</sup> As more antimicrobials were discovered throughout the years, we saw with almost mechanical regularity the appearance of strains resistant to these newly discovered drugs, with rates increasing the more these antibiotics were used. As the drug pipeline dried up and fewer novel molecules were discovered, attention now turned to ensuring that these antimicrobials were used judiciously.

A 2014 report from the United Kingdom on antimicrobial resistance (AMR) estimated that there will be 10 million people dying every year from resistant bacteria by the year 2050 if nothing is done about it today.<sup>2</sup> By then, the worldwide cost related to AMR is projected to be as much as US\$100 trillion. The magnitude of AMR’s effect on people and economies led the World Health Assembly to endorse a Global Action Plan on AMR. Soon, AMR appeared on the agenda of almost every nation, including the Philippines. The 2018 Antimicrobial Resistance Surveillance Program (ARSP) report presents the sobering reality that AMR is present in the Philippines as well (Figure 1). It is but fitting that all physicians should pay attention to this important crisis.

The main driver of antibiotic resistance is antibiotic consumption, whether appropriately or inappropriately prescribed. Sun et al has demonstrated that the occurrence of resistant *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* follows the curve of antibiotic prescriptions for aminopenicillins and fluoroquinolones, respectively, with a lag of about one month (Figures 2A & 2B).<sup>3</sup> In short, physician prescriptions directly affect resistance rates. While there are many different factors that affect AMR,<sup>4</sup> the clearest and most direct one is antimicrobial consumption. It is then incumbent upon all physicians to be careful about how they use antibiotics and should consider these medicines a precious resource. This need to rationalize the use of antimicrobials is what antimicrobial stewardship (AMS) is all about.

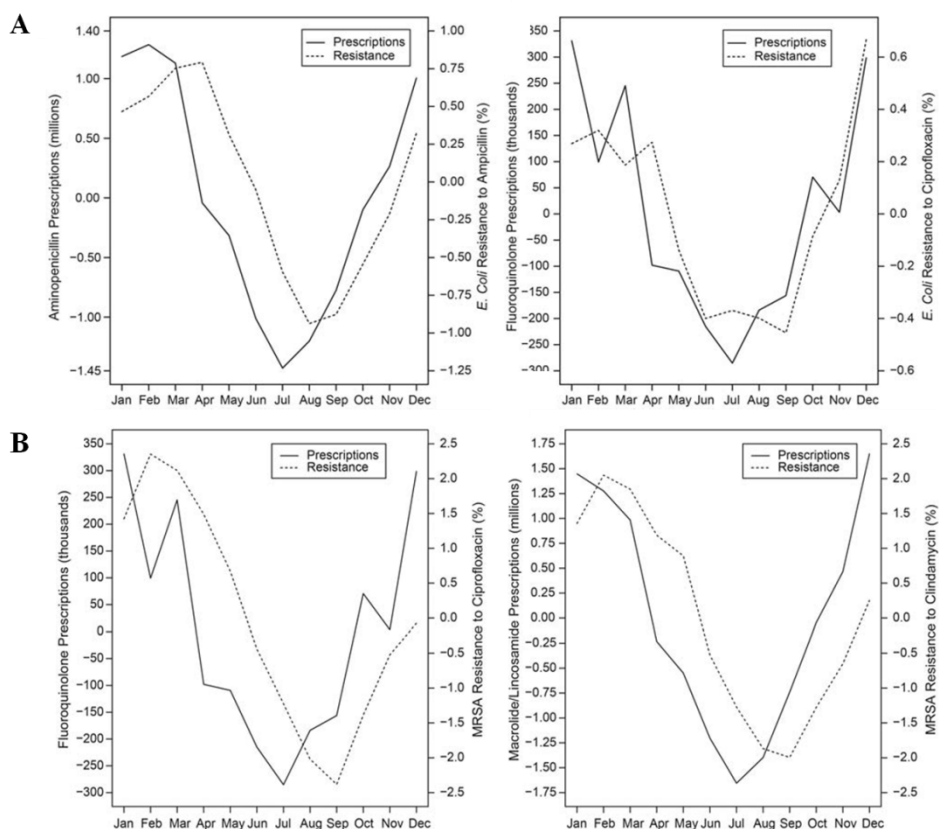


**Figure 1.** Carbapenem resistance of *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (all isolates) as reported in the Antimicrobial Resistance Surveillance Program (ARSP) from 2009 to 2018. The reported carbapenem for *A. baumannii* is imipenem due to unavailability of meropenem susceptibility in the earlier reports

The Medical City (TMC) started restricting access to very broad-spectrum antimicrobials in the late 1990s. This early attempt at improving antimicrobial use is evidence of TMC’s pioneering leadership role in AMS in the country. In response to the global call against AMR, our own government published the Philippine Action Plan to Combat Antimicrobial Resistance: One Health Approach in 2016.<sup>5</sup> Soon thereafter, the Department of Health required all hospitals in the country to create formal Antimicrobial Stewardship Programs (ASPs) as a requirement for licensing and accreditation. Since TMC already had many initiatives in place that promoted antimicrobial stewardship, the creation in 2016 of a formal Antimicrobial Stewardship Committee focused on consolidating and expanding AMS activities was a logical step

## Antimicrobial Stewardship: Definition and Rationale

Good AMS is a “practice that ensures the optimal selection, dose, and duration of an antimicrobial therapy that leads to the best clinical outcome for the treatment or prevention of infection while producing the fewest toxic effects and the lowest risk for subsequent resistance.”<sup>6</sup> The fundamental challenge in AMS is the balancing act between providing timely and appropriate empirical broad spectrum antimicrobial therapy for individual patients versus reducing unnecessary use of these same agents and their subsequent collateral damage.<sup>7,8</sup>



**Figure 2.** (A) Seasonal pattern of high-usage antibiotic prescriptions and *Escherichia coli* (*E. coli*) resistance, showing 1-month lag; (B) Seasonal pattern of antibiotic prescriptions and Methicillin-Resistant *Staphylococcus aureus* (MRSA), showing 1-month lag. Figures reprinted with permission from Oxford University Press (Sun *et al.*, Seasonality and Temporal Correlation between Community Antibiotic Use and Resistance in the United States, 2012, 55(5): 690-691)

Schuts *et al* examined the existing evidence for 9 AMS objectives using four pre-defined outcomes: clinical outcomes (mortality and morbidity), adverse events, cost, and resistance rates.<sup>9</sup> While they cite generally low quality of evidence and moderate to high heterogeneity between studies, they found that guidelines-based empirical therapy, de-escalation of therapy, switch from intravenous to oral treatment, therapeutic drug monitoring, antimicrobial restriction, and bedside consultation resulted in significant benefits for one or more of the 4 outcomes.

Honda *et al* examined inpatient AMS in the Asia Pacific Region.<sup>10</sup> Using 4 outcomes (clinical, antimicrobial prescription, microbiology, and expenditure), the authors reviewed the results of 46 studies from 9 countries. Their meta-analysis demonstrated that ASPs resulted in significant reductions in antimicrobial and carbapenem consumption and trends toward decreased incidence of multidrug-resistant organisms and antimicrobial expenditure. Consistent with the previous reviews, this study showed no significant mortality increase with ASPs.

The most recent Cochrane Review of hospital-based interventions to improve antibiotic prescribing practices<sup>11</sup> showed that enabling and restrictive methods were

associated with a 15% increase in compliance with desired practice, a 1.95-day decrease in treatment duration, and a 1.12-day decrease in inpatient length of stay without compromising patient safety.

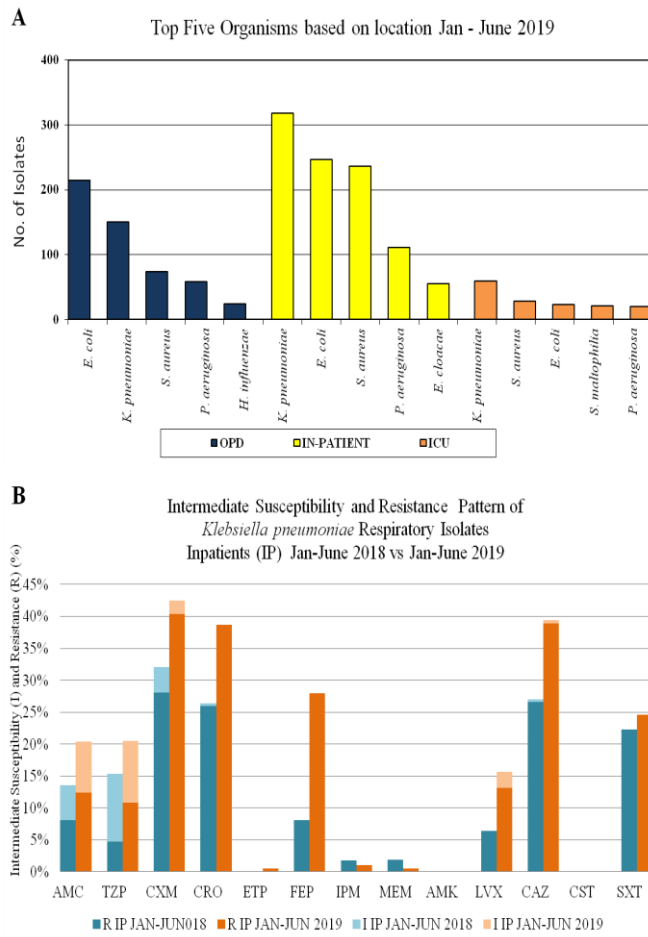
### Components of the TMC Antimicrobial Stewardship Program

In November 2017, the leadership of TMC approved the policy governing all aspects of antimicrobial utilization in our institution. The policy was patterned after the DOH's own Manual of Operations for Antimicrobial Stewardship,<sup>12</sup> with revisions meant to adopt various components to the culture of TMC. Some of the most practical components of the program, as well as its objectives, are described below.

**TMC Antimicrobial Use Guidelines (Empiric Recommendations, Surgical Prophylaxis).** The hospital's antibiogram is one of the most important tools used in AMS. Aside from informing physicians about which organisms are most common in the hospital, classified by source (blood, urine, respiratory secretions, etc) and by location (outpatient, inpatient wards, and critical care units, (Figure 3A), the antibiogram also reports on susceptibility patterns of these organisms (Figure 3B). The idea is to allow the physicians to make educated decisions about

empiric therapy for individual patients. At TMC, the information from the local antibiogram is synthesized with the recommendations from the National Antibiotic Guidelines Committee (NAGCOM), a multidisciplinary group of experts tasked to review existing local and international guidelines and formulate a unified document to be used by healthcare institutions in the country.<sup>13</sup> The resulting document, TMC’s Antimicrobial Use Guidelines, is reviewed and published annually (Table 1) to guide physicians in the management of the most common infections and in making wise choices for surgical antibiotic prophylaxis.

**Drug Duration Audit and Feedback (DDAF or Automatic Stop Order).** There is a growing body of evidence that for most infections, a short course of antimicrobials is as effective as the traditional longer courses.<sup>14</sup> Short courses of antimicrobials result in less adverse effects, such as *Clostridioides difficile* infections, lower cost, and better outcomes. The DDAF is our attempt to remind the medical staff to frequently evaluate the need for continued antibiotics in individual patients. DDAF is currently in effect only in critical care units but will soon be implemented hospital-wide in accordance with directives from the DOH.



**Figure 3.** (A) Seasonal TMC Antibiogram January to June 2019, top 5 organisms by hospital location; (B) TMC Antibiogram, intermediate susceptibility and resistance patterns of *Klebsiella pneumoniae* (respiratory isolates obtained from inpatients); AMC- amoxicillin-clavulanic acid, TZP- piperacillin-tazobactam, CXM- cefuroxime; CRO- ceftriaxone, ETP- ertapenem, FEP- cefepime, IPM- imipenem, MEM- meropenem, AMK- amikacin, LVX- levofloxacin, CAZ- ceftazidime, CST- colistin, SXT- trimethoprim-sulfamethoxazole

**Prospective Audit of Monitored Antimicrobials with Direct Feedback.** TMC was one of a handful of Philippine hospitals participating in the Global Point Prevalence Survey on Antimicrobial Consumption and Resistance.<sup>15</sup> In this survey, we found that 53% of inpatients at our institution are on antimicrobials at any given time.<sup>16</sup> This is a staggering figure since worldwide average is only around 31%.<sup>17</sup> In addition, 43% of our antimicrobial usage did not adhere to NAGCOM guidelines. In an attempt to optimize utilization of antimicrobials at the point of care, the HICEC Executive Committee created a list of 8 “monitored” antimicrobials derived from the most commonly used antibiotics based on the results of our prevalence survey. Prescription of these monitored antimicrobials will trigger the AMS Team (composed of the AMS Committee Chair or ID fellow and AMS clinical pharmacists) to review the patient’s chart and to make one or more of the following recommendations: intravenous-to-oral therapy switch, dose optimization, and streamlining or de-escalation. Implementation of this initiative will be in phases and will begin with one or more medical floors with plans for hospital-wide expansion.

**Prior Approval of Restricted Antimicrobials (PARA).** This stewardship initiative has been in place in one form or another since the late 1990s. In its current form, the list of restricted antimicrobials include: amphotericin B, anidulafungin, cefepime, colistin (polymyxin E), daptomycin, ertapenem, ganciclovir, imipenem, linezolid, meropenem, polymyxin B, tigecycline, valganciclovir, and vancomycin. Prescription of these medications by a non-ID physician must be accompanied by documentation of approval from an ID consultant. This will ensure that the broadest spectrum antimicrobials (and hence the most precious) are used appropriately and judiciously. This stewardship initiative is implemented hospital-wide.

**Table 1.** The Medical City Empiric Antimicrobial Recommendations 2019

<b>Pneumonia</b>	
Community-acquired pneumonia- MODERATE RISK	
-	Ampicillin-sulbactam 1.5g IV every 6 hours OR
-	Ceftriaxone 2g IV once a day
	PLUS
•	Azithromycin 500mg PO once a day OR
•	Clarithromycin 500mg PO twice a day OR
•	Levofloxacin 750mg PO once a day
Community-acquired pneumonia- HIGH RISK, without risk factors for <i>P. aeruginosa</i>	
-	Ceftriaxone 2g IV once a day OR
-	Ertapenem 1 g IV once a day
	PLUS
•	Azithromycin dehydrate 500mg IV once a day OR
•	Levofloxacin 750mg IV once a day
Community-acquired pneumonia- HIGH RISK, WITH risk factors for <i>P. aeruginosa</i>	
-	Piperacillin-tazobactam 4.5g IV every 6hours OR
-	Cefepime 2 g IV every 8-12h
	PLUS
•	Azithromycin 500mg IV once a day
	PLUS
•	Amikacin 15mg/kg IV once a day
Community-acquire pneumonia- HIGH RISK with suspicion of MRSA, ADD:	
-	Vancomycin 25-30 mg/kg IV loading dose then 15-20 mg/kg every 8-12 hours OR
-	Linezolid 600mg IV every 12 hours OR
-	Clindamycin 600mg IV every 8 hours
HAP/ VAP- inpatient, no risk factors for MDR organisms (e.g. <i>A. baumannii</i> )	
-	Piperacillin-tazobactam OR Cefepime OR Meropenem ±
-	Amikacin 15mg/kg IV once a day
Pneumonia other than CAP- inpatient with risk factors for MDROs (e.g. <i>A. baumannii</i> )	
-	Immediate referral to ID recommended
Pneumonia other than CAP- inpatient, non-ICU, with risk factors for MRSA or aspiration	
-	Add Clindamycin
Pneumonia other than CAP- inpatient, ICU with risk factors for MRSA	
-	Add Vancomycin OR Linezolid
<b>Urinary Tract Infections</b>	
Acute cystitis	
-	Nitrofurantoin
Acute uncomplicated pyelonephritis	
-	Ceftriaxone
In-patients (hospital acquired):	
-	Without risk factors for ESBL producing organisms:
•	Piperacillin-tazobactam OR Amikacin
-	With risk factors for ESBL producing organisms:
•	Ertapenem OR Amikacin
<b>Skin and Soft Tissue Infections</b>	
Caveat: the vast majority of non-purulent SSTI (i.e. no microbiologic data available) is due to Streptococci	
Community acquired, localized, without signs of sepsis:	
-	Clindamycin OR
-	Doxycycline OR
-	Cotrimoxazole (no good Streptococcal coverage)
Nosocomial and/ or with signs of sepsis:	
-	Vancomycin OR
-	Linezolid
	PLUS
•	Piperacillin-tazobactam
<b>Azithromycin FDA Drug Safety Communication</b>	
1.	FDA warns about increased risk of cancer relapse with long term use of azithromycin after donor stem cell transplant (8/3/2018)
2.	Azithromycin and the risk of potentially fatal heart rhythms (3/12/2013)
<b>Levofloxacin FDA Drug Safety Communication</b>	
1.	FDA warns about increased risk of ruptures or tears in the aorta blood vessel in certain patients (12/20/2018)
2.	FDA is strengthening the current warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decrease in blood sugar and certain mental health side effects (7/10/2018)

### Future Direction

Except for the PARA initiative, implementation of the components of the AMS program are in place only in selected areas of the hospital. In order to ensure that TMC remains a good steward of these precious antimicrobials and maintain its leadership in this field, the program components have to be implemented hospital-wide. For this to occur, hospital leadership needs to invest in the hiring and training of additional staff (both clinical pharmacists and nurses) with a heart for AMS. Transitioning to a new electronic record with the capacity to automatically generate AMS-related reports should also allow the AMS team to streamline its workflow and devote more time to interacting with the medical teams (i.e. audit and feedback) rather than tedious data collection.

With a national government bent on ensuring implementation of an AMS program nationwide in the next few years, there is a flurry of activity in both the public and private sectors to ensure compliance with newly established policies. For many healthcare institutions, especially the smaller hospitals unfamiliar with the concepts of AMS, this means sending staff to training seminars and multiple strategic planning sessions. Because our institution has invested in AMS for many years, we find ourselves in a somewhat mentorship role in the midst of all this activity. Beginning in 2016, some of our leaders in the Section of Infectious Diseases have been heavily involved in the DOH-sponsored training of hospitals in AMS. In 2016, we hosted two clinical pharmacists in the maiden run of a clinical pharmacy fellowship for AMS. It is evident that our commitment to building the national AMS program is resolute and our role in the national AMS program is an embodiment of our hospital's mission to take a leadership role in shaping how the nation thinks, feels, and behaves about health.

More than all the AMS-related programs and policies in place, the core need of a good antimicrobial stewardship campaign is behavioral change and a paradigm shift among antibiotic prescribers. AMR has been called a “slow moving catastrophe<sup>4</sup>” because it is less acute and less glamorous than ebola or epidemic influenza. But AMR is just as deadly. The families of patients affected by infections caused by multidrug resistant organisms (MDROs) know all too well how lethal these bacteria can be. There is a mountain of evidence showing that antibiotics are overprescribed and abused, despite well-written, evidence-based guidelines. Unless antibiotic prescribers stop thinking small (i.e. just their own patients) and start thinking with a global mindset, antibiotics will continue to be overused. There are many different things physicians can do to reduce inappropriate antibiotic use.<sup>4</sup> The common theme in all these should be a basic understanding of why things need to change.

Antibiotics are one of the most commonly prescribed types of medication and their use cuts across all specialties. If we lose this precious resource to over-prescription and abuse, we may bring the world back to an era when penicillin was unavailable, and patients died from the simplest of infections. All physicians must recognize their critical role as stewards of antibiotics and should work to ensure that these drugs are used properly and judiciously.

**THE MEDICAL CITY ANTIMICROBIAL STEWARDSHIP TEAM**

**Chair:** Karl Evans R. Henson, MD

**AMS Specialist:** Maria Katrina D. Rayos, RPh

**Senior Stewardship Consultant:** Mediadora C. Saniel, MD

**Infectious Disease Consultants:**

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 Mary Ann D. Lansang, MD  
 Regina P. Berba, MD  
 Marissa M. Alejandria, MD  
 Cybele Lara R. Abad, MD  
 Raul V. Destura, MD  
 Marja B. Buensalido, MD  
 Cynthia A. Aguirre, MD  
 Sarah R. Makalinaw, MD

**Infectious Disease Fellows:**

Jan Jorge M. Francisco, MD  
 Jia An G. Bello, MD

**Clinical Pharmacists:**

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 Clarissa Jane S. Sarmiento, RPh  
 Molyn B. Nunez, RPh  
 Raquel Guia Grace C. Macaparra, RPh

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## Featured TMC Publication

# Specific Stressors Relate to Nurses' Job Satisfaction, Perceived Quality of Care, and Turnover—The Nurse Manager's Perspective

In this feature, we asked The Medical City Ortigas' Nurse Manager for General Nursing Unit, Ms. Percy Aiggie S. Lauria, RN, MAN, co-author of this paper published in the International Journal of Nursing Practice, to answer some of our questions on how they arrived in studying a controversial yet important aspect of nursing service—the stressors affecting the nurse's job satisfaction, perceptions and service turnover.

### **TMC Journal (TMCJ):**

Was there a main trigger/event that led to the research study? If so, what was it?

### **Ms. Lauria (PAL):**

*It was in late 2016 when the nurse turnover rate went beyond the acceptable rate of 10% per Business Daily Pay on Healthcare industry. As nurse leaders, we have to understand the reason for this rate and intervene accordingly. During our brainstorming, we decided to focus on stressors that might contribute to nurse turnover. Specifically, we want to examine what stressor is the most frequently reported and create programs or policies that would mitigate such stressor. On the other hand, embarking on a research study is long been overdue for the Nursing Services Division. It was a perfect timing when Dr. John Robert Bautista (a Filipino nurse who was then finishing his PhD at Nanyang Technological University in Singapore) assisted us in conducting the study as a consultant. Moreover, we did the study because there is a lack of "published" literature on stress and its association with specific nurse outcomes in the Philippines.*

### **TMCJ:**

How long have you worked as a registered nurse?

### **PAL:**

*I am already going 19 years in practice since I finished my BSN at Western Mindanao University in 1999. At age 19, after obtaining my RN license, I flew to Manila and was accepted for a job in The Medical City in December 2000. I started as a staff nurse, promoted to Charge Nurse, Head Nurse, Supervisor and now as a Nurse Manager of 14 General Nursing Units and assisting the Chief Nurse in his administrative functions.*

### **TMCJ:**

In the paper, you mentioned that some registered nurses chose not to practice the profession. Personally, what do you think made you choose to practice nursing despite the aforementioned stress factors?

### **PAL:**

*In my case, I knew exactly what I want in my life and career. And I agree with what our CEO, Dr. Eugene Ramos, shared with us: I believe that finding that purpose, pleasure, and pride in the nursing profession and workplace is the key.*

### **TMCJ:**

In the local setting and in the present time, aside from the nine-factor stressors used in the study, what other factors do you think can also affect nurses' job satisfaction, perceived quality of care, and turnover intention?

### **PAL:**

*I think the amount of "compensation and benefits" can also affect nurses' job satisfaction, quality of care provided to patients, and turnover intention. We need to understand what comprises a decent standard of living for new nurses, especially those coming from the provinces and have tried their luck in the Metro. Likewise, career prospects inside the institution might also be a contributing factor to turnover intention. To mitigate this, we launched TMC's Career Track and Specialization program. As our COO, Atty. Martin P. Samson, said, "While the grass is green on the other side of the fence, the GRASS IS GREENER WHERE YOU WATER IT."*

### **TMCJ:**

With the results of the study, what specific changes or programs do you think would benefit the institution?

### **PAL:**

*We need to expedite the review of patient chart forms to reduce data duplication and unreasonable documentation. If not, we hope to fully transition from paper to computerized documentation, especially are portion of the nursing forms. A structured manpower computation not only based on occupancy rate but also on patient acuity, staff leave and training might address issues on heavy workload due to inadequate staffing.*

**To access the recently published article of TMC's Nursing Services Division, please check on: Bautista, JR, Lauria, PAS, Contreras, MCS, et al. Specific stressors relate to nurses' job satisfaction, perceived quality of care, and turnover intention. Int J Nurs Pract. 2019;e12774. <https://doi.org/10.1111/ijn.12774>.**

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YOU  
HAVE  
INNOVATIVE  
IDEAS  
THAT  
CAN  
BE  
LIFE-SAVING  
AND  
REWARDING ?**





# THE MEDICAL CITY VENTURES OFFICE

## WHO WE ARE

The Medical City Ventures Office (TMCVO) is the technology transfer arm of The Medical City (TMC). It aims to protect and utilize Intellectual Properties (IP) developed by research projects funded through TMC and assist TMC researchers on the best means to protect and commercialize these IP's.

## WHAT WE DO

We provide assistance in the protection of your inventions through patent and utility model applications and your software/ programs through copyright registrations.

Our office also conducts customer discovery process to help you plan best to prepare your technology for commercialization.

## TALK TO US

Ready to talk about your innovation?  
Contact Mr. Cedrik Ben Gayares of TMCVO at [cagayares@themedicalcity.com](mailto:cagayares@themedicalcity.com) for more details on how we can provide our services to you.



# Guidelines for Submission to The Medical City Journal

## GENERAL GUIDELINES

1. The Medical City (TMC) Journal is the official research publication of TMC-CTRI. The CTRI believes that research within TMC and any of its networks should be known to the public and to other researchers to help advance the medical field. As such, the following guidelines shall apply:
  - a. CTRI shall announce a specified date to open manuscript submission for publication. Staff, fellows, residents allied health professionals, and/ or students in TMC shall be required to submit an original manuscript. In case the manuscript is already published or submitted to another journal, a letter and proof of acceptance/ submission shall be submitted to the Science Research Specialist (mbcarascal@themedicalcity.com) for acknowledgement.
  - b. The authors shall be responsible for adhering to the format and guidelines provided by the CTRI. Publication format and guide to authors shall be provided in the website (please refer to the guidelines below).
  - c. The authors shall submit the manuscript and necessary attachments to mbcarascal@themedicalcity.com.
  - d. A notice of acceptance/ revision/ rejection shall be sent to the corresponding author
    - i. A letter of acceptance shall contain a remark indicating that the manuscript shall be included in the publication (please refer to Attachment U for sample format).
    - ii. A letter of revision shall contain comments, suggestions and remarks from peer reviewers and the editors that the author may consider for the manuscript to be included in the publication (please refer to Attachment V for sample format).
    - iii. A letter of rejection shall contain reasons for the editor's decision to not include the paper in the publication (please refer to Attachment W for sample format).
  - e. The authors shall be responsible for providing the necessary revisions as advised by The Medical City Journal Editorial Board. A point by point response to the editor shall be submitted together with the edited manuscript. Revised manuscript and attachments shall be submitted to mbcarascal@themedicalcity.com based on the deadline set by the CTRI.
  - f. The CTRI shall ensure that TMC journal be made available/ published in electronic and softbound forms
  - g. Submission of all manuscript shall be made online. No hardcopy submission or email submission shall be entertained unless advised by the editors.
  - h. A corresponding author with a valid email address shall be assigned for each submitted paper. The corresponding author will be the contact person of the CTRI for the issuance of letters for approval, revision or rejection of the submitted manuscript.
2. The document should be saved in .doc or .docx format. The filename for first time submission should be as follows:

*Primary Author's Last Name (put et. al if many authors)\_Year of submission\_Category (Original Article/ Case Repot/ Review/ Updates)\_Journal/ Proceedings.docx*

The filename for revised manuscript should be as follows:

*Revision Revision Number (1,2,3..) Primary Author's Last Name (put et. al if many authors)\_Year of submission\_Category (Original Article/ Case Repot/ Review/ Updates)\_Journal/ Proceedings.docx*
3. In case of revisions, the comments of the editors must be addressed point by point by the authors in a separate document. For comments from the editors not considered by the author, justification must be provided. The document for revision shall be considered an attachment and should be named *Comments\_Revision\_Primary Author's Last Name\_Year of Submission*. Two copies of the revised manuscript should be submitted – a clean copy and a copy with changes tracked/ marked.

## Formatting Guidelines (Original Article):

1. Submitted manuscript shall be formatted on a short bond paper (US Letter Paper Size: 8.5 x 11 inches), with 1 inch margin on all sides, with continuous line number, double spaced, font style is Times New Roman, size 12. Manuscript should have page numbers starting from 1.
2. The manuscript shall be arranged as follows: title page, abstract, manuscript body, acknowledgement, references, tables and figures.
3. The following shall be the content of the specific sections of the manuscript:

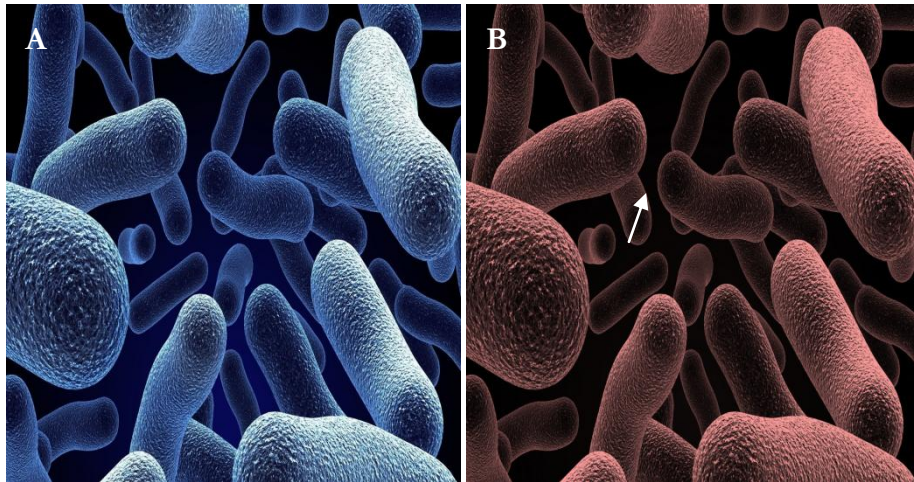
- a. Title Page: Complete title of the article, name of the authors (Last name, First name/s, Middle initial; should not include any post-nominal titles), affiliations of the authors (include only the current departmental or institutional affiliation of the author), Financial support (if applicable)
  - Note: Each author must have an affiliation. Affiliations can be associated or tagged to the author using a number superscript. After the listing of the names of the authors, the affiliations shall follow and be listed in order of its association to the authors (i.e. arranged starting from 1)
- b. Abstract: The abstract shall not be more than 250 words. The abstract shall contain the main objective, methodology, results and conclusion. Do not put any citations in the abstract.
- c. Manuscript Body: The text shall have no more than 3000 words excluding the legends, tables and figure titles, table contents, acknowledgement and references. Metric units shall be used for all measurements. P values and other statistical measurements (if applicable) shall be expressed in 3 decimal places and shall be rounded off as applicable. Abbreviation of a term can only be applied if the term is used at least three times in the text (excluding the abstract). Footnotes shall not be used within the body of the text. Subsections within each of the section of the text can be used as appropriate. For the succeeding subheadings, the following styles shall be used:
  - HEADING** capital letters, bold
  - Subheading 1** first letter is capitalized, bold
  - Subheading 2* first letter is capitalized, bold, italicized
  - Subheading 3 first letter is capitalized
- d. Acknowledgements: Acknowledgement section shall be brief and with permission obtained from those acknowledged.
- e. References: Reference list and in-text citations shall follow the guidelines from the American Psychological Association (APA). A summary of the rules can be accessed in this link: <https://owl.english.purdue.edu/owl/resource/560/01/>
- f. Tables: All tables must be placed after the references section. Tables shall be labeled consecutively in order of its citation in the manuscript. Table titles shall be placed at the top of the table. Table number shall be in bold while table description shall be in normal configuration. Texts for the table contents shall use a font size of 10 and is double spaced. Abbreviations and additional notes can be defined in a footnote. Superscript lowercase letters (a-z) shall be used for the footnotes. Tables shall not be saved as an image. As an example, a Table should appear as follows:

**Table 1.** The table required for this sample

<b>Table Title</b>	<b>Content</b>
Table 1 <sup>a,b</sup>	The table required for this sample
Table 2	The table required for this sample
Table 3	The table required for this sample

- a- this refers to the notes for a specific item in the table
- b- this refers to the notes for a specific item in the table

- g. Figures, Images, Illustrations: All figures should be found after the tables section. Titles of the figures should be placed at the bottom. It should be brief and informative. Figure number shall be in bold while figure description shall be in normal configuration. Related or collage of figures should be labeled with A, B, C, etc. This should be described in the title of the figure. Structures/ items/ part of the photo that should be emphasized can be pointed using an arrow. Pictures should be of high quality while graphs should be in scalable vector format. Only a maximum of two figures should be found in one page. For photomicrographs, specify staining procedure and magnification (or the equivalent measurement of the bar in case a scale bar was used). Figures should be in the following format:



**Figure 1.** The figure required for this sample. (A) Bacteria in blue color. (B) Bacteria in red color. The arrow refers to the emphasized structure

4. For more information on how to write original articles, you may access this link: [http://abacus.bates.edu/~ganderso/biology/resources/writing/HTW\\_Guide\\_Sections\\_3-7-2011.pdf](http://abacus.bates.edu/~ganderso/biology/resources/writing/HTW_Guide_Sections_3-7-2011.pdf)

#### **Formatting Guidelines (Case Reports):**

1. Submitted manuscript shall be formatted on a short bond paper (US Letter Paper Size: 8.5 x 11 inches), with 1 inch margin on all sides, with continuous line number, double spaced, font style is Times New Roman, font size is 12. Manuscript should have page numbers starting from 1.
2. Publication priority is given to cases which meets one or more of the following criteria:
  - a. a first-of-its-kind, unexpected, or unusual observation
  - b. a new disease
  - c. a previously unknown manifestation of a disease
  - d. a new pathophysiology of a disease
  - e. new observation of adverse event
  - f. new therapeutic activity of treatments
3. Case report contents are not strictly structured but shall contain, at the least, a title page, unstructured abstract, manuscript text, consent, acknowledgement and references.
4. The following content shall be the content of the report (if applicable):
  - a. Title Page: Complete title of the article, name of the authors (Last name, First name/s, Middle initial; should not include any post-nominal titles), affiliations of the authors (include only the current departmental or institutional affiliation of the author), Financial support (if applicable)
    - Note: Each author must have an affiliation. Affiliations can be associated or tagged to the author using a number superscript. After the listing of the names of the authors, the affiliations shall follow and be listed in order of its association to the authors (i.e. arranged starting from 1)
  - b. Abstract: The abstract shall not be more than 250 words.
  - c. Manuscript Text: The main text shall be approximately 800-1800 words only. Ideally, it shall contain the following sections:
    - Introduction/ Background
    - Case Presentation
    - Discussion
    - Conclusion
    - Patient's Perspective
  - d. Consent: This section shall provide a statement to confirm that a consent was given by the patient for the consent to be published in The Medical City Journal.
  - e. Acknowledgements: Acknowledgement section shall be brief and with a permission obtained from those acknowledged.



- f. References: Reference list and in-text citations shall follow the guidelines from the American Psychological Association (APA). A summary of the rules can be accessed in this link: <https://owl.english.purdue.edu/owl/resource/560/01/>
5. Case reports shall have no more than two tables or two figures in its entirety. Table and Figure formatting is the same as with the guidelines for the original articles.
6. For more information on how to write case reports, you may access this link: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879062/pdf/1752-1947-7-239.pdf>

**Formatting Guidelines (Review Article, Concise Review, Meta-Analysis):**


1. Submitted manuscript shall be formatted on a short bond paper (US Letter Paper Size: 8.5 x 11 inches), with 1 inch margin on all sides, with continuous line number, double spaced, font style is Times New Roman, font size of 12. Manuscript should have page numbers starting from 1.
2. Review articles are not strictly structured. However, contents shall consist of 2500-5000 words excluding the abstract and references.
3. Title Page: Complete title of the article, name of the authors (Last name, First name/s, Middle initial; should not include any post-nominal titles), affiliations of the authors (include only the current departmental or institutional affiliation of the author), Financial support (if applicable)
  - Note: Each author must have an affiliation. Affiliations can be associated or tagged to the author using a number superscript. After the listing of the names of the authors, the affiliations shall follow and be listed in order of its association to the authors (i.e. arranged starting from 1)
4. The Abstract is unstructured and shall not be more than 250 words.
5. Review articles shall have no more than five tables and figures in its entirety. Table and Figure formatting is the same as with the guidelines for the original articles.
6. References: Reference list and in-text citations shall follow the guidelines from the American Psychological Association (APA). A summary of the rules can be accessed in this link: <https://owl.english.purdue.edu/owl/resource/560/01/>
7. The review article shall provide 3-5 takehome points for the readers
8. For more information on how to write review articles, you may access this link: [https://www.academia.edu/30757379/How\\_to\\_Write\\_Review\\_Article](https://www.academia.edu/30757379/How_to_Write_Review_Article)

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