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This article aims to analyze the availability, access, and affordability of medications for children with advanced Chronic Kidney Disease (CKD) treated with hemodialysis (HD) in a low to middle income country (LMIC). A cross-sectional chart review was carried out to determine the most common medications used in an HD pediatric unit, including medication name, dose, frequency, dosage form, and route of administration. Two pharmacies within the hospital perimeter, one public and one private, were consulted to determine medication cost and availability for generic and brand-name equivalents. From 30 patients attending the HD unit, 22 records were reviewed. Overall, 94 % of brand name medications were available at pharmacies consulted, versus 52% of generic medications. In public pharmacies, 41% of brand name, and 29% of generic medications were available. The average cost for a full month's treatment for brand name drugs in the private pharmacy was 495.00 USD versus 299.00 USD in the public pharmacy. For generic drugs, the average cost was 414.00 USD, and 239.00 USD in private and public pharmacies respectively. On average, brand-name drugs in the private pharmacy cost 41 days' wages versus 25 in the public pharmacy. Generic drugs in the private pharmacy cost 34 days' wages versus 20 in the public pharmacy. Overall, there was limited access to generic medications, medications had an overall high cost compared to other countries both of which have the potential to impact treatment adherence and overall outcomes of CKD5 pediatric patients in Guatemala. This reality can be translated to other LMIC.

Keywords: Chronic kidney disease, pediatric hemodialysis, medication access, medication availability, affordability, Guatemala.

El artículo tiene como objetivo analizar la disponibilidad, acceso y asequibilidad de los medicamentos para niños con Enfermedad Renal Crónica (ERC) en tratamiento con hemodiálisis (HD) en un país de bajos a medianos ingresos. Se llevó a cabo un estudio transversal para determinar los medicamentos más utilizados en una unidad de hemodiálisis pediátrica, incluyendo el nombre del medicamento, dosis, frecuencia, forma farmacéutica y vía de administración. Dos farmacias dentro del perímetro del hospital, una pública y una privada, fueron consultadas para determinar el costo

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y disponibilidad de medicamentos genéricos y de marca. De un total de 30 pacientes de la unidad de hemodiálisis, 22 expedientes fueron revisados. En general 94% de marca se encontraban disponibles en las farmacias consultadas en comparación a un 52% de los medicamentos genéricos. En farmacias públicas, 41% de medicamentos de marca y 29% de medicamentos genéricos se encontraban disponibles. El costo promedio para un mes de tratamiento con medicamentos de marca adquiridos en una farmacia privada era de \$495.00 vs \$299.00 en una farmacia pública. Para medicamentos genéricos, el costo promedio correspondía a \$414.00 y \$239.00 en farmacias privadas y públicas respectivamente. En promedio, los medicamentos de marca adquiridos en una farmacia privada requieren 41 días de trabajo en un mes a comparación de 25 días si se adquieren en una farmacia pública. Los medicamentos genéricos adquiridos en farmacias privadas corresponden a 34 días de trabajo vs 20 días en farmacias públicas. En general existió un acceso limitado a medicamentos genéricos y los medicamentos poseen un costo general más elevado a comparación de otros países lo que implica un posible impacto en la adherencia terapéutica y los padecimientos secundarios de la ERC en los pacientes pediátricos en Guatemala. Esta realidad se puede aplicar a otros países de bajos a medianos ingresos.

Palabras clave

Enfermedad renal crónica, Hemodiálisis, Pediatría, Acceso a medicamentos, Disponibilidad de medicamentos, asequibilidad, Guatemala.

Introduction

Chronic Kidney Disease (CKD) is a major public health problem worldwide (Harambat et al., 2012) yet there are few CKD registries documenting the burden and costs of care in low- and middle-income countries (LMICs). According to the report presented in 2017 by the Latin-American Society of Nephrology and Hypertension (SLANH), the prevalence of kidney replacement therapy (KRT) increased from 601 per millions of people (pmp) in 2012 to 660 pmp 2013 (Gonzalez-Bedat et al., 2017).

Guatemala is a Central American country where nearly half the population is indigenous Maya living in rural agricultural communities where there is limited access to medications. Prior research on access to medicines in Guatemala suggests that medications used to treat chronic disease are often unaffordable, and in some cases, unavailable (Flood et al., 2017). Surveys have shown that the cost of many medications is higher in Guatemala compared to international reference prices reflecting disparities on access to medicine (Flood et al., 2017; Emmerick et al., 2013). In Guatemala, where 59.3% of the population is below the poverty line (Instituto Nacional de Estadística [INE], 2015), patient's families are directly affected by high medication prices. This is of particular concern for pediatric patients with chronic diseases where extra costs pose a significant burden on the families economic wellbeing.

Advanced CKD affects hundreds of children in Guatemala (prevalence 4.9 children per million age-related population) (Fagan, 2017; Cerón et al., 2021) requiring many supportive treatments besides KRT, including medications for hypertension, calcium phosphorus metabolism, and for treatment of anemia such as erythropoietin (Quigley, 2012). In some cases, additional medications are often needed such as anticonvulsants, vitamin supplements and laxatives. The cost of medications in Guatemala is disproportionately high compared to international reference prices (Management Sciences for Health, 2016), although the magnitude of these challenges for children with renal disease in Guatemala is poorly defined.

The Ministry of Public Health and Social Assistance (MSPAS) provides health care to 70% of the population in Guatemala, in addition to the Guatemalan Social Security Institute (IGSS), which offers coverage to less than 17.45% of the population linked to formal employment. Public institutions in Guatemala have struggled to guarantee access to equitable, high-quality health services compared to other Central American countries. Overall, there is low public financing of health services to effectively provide care to Guatemalan citizens (Rojas, 2009). Nevertheless, the government has taken steps to address medication needs and transparency in procurement processes within the public health sector. For example, MSAPS created the Medication Accessibility Program (PROAM in Spanish), to promote access and affordability of high-quality medicines but the lack of supportive legislation, economic inflation, and political issues that affect the country, have prevented the regulation of drug prices (Roman, 2020).

FUNDANIER (Fundación para el Niño Enfermo Renal) is the primary provider of services for children with CKD in Guatemala. It is a public-private collaboration between FUNDANIER and the MSPAS, and is based at Hospital Roosevelt (Garcia et al., 2020. Cerón et al., 2014) in Guatemala City. It has a hemodialysis (HD) unit that treats an average of 35 pediatric patients monthly (Garcia et al., 2020). Each patient receives HD sessions 2 or 3 times per week, each session has a cost of 121USD, which is paid by the program. Patients also receive medications such as erythropoietin and alphacalcidol which are donated to patients by FUNDANIER. Most patients attending FUNDANIER obtain medications through the public pharmacy located on the hospital premises within a 5-minute walk of the clinic. Some patients obtain medications from private pharmacies, with the closest private pharmacy chain located within a 15-minute walk from the clinic. This private pharmacy chain has presence throughout the country and may be accessed by patients who reside in provinces outside of Guatemala City.

To better understand the economic impact of medication cost for families of children with CKD in Guatemala, we carried out a cross sectional chart review and pharmacy-based survey to explore the cost, availability and affordability of medications. We aimed to generate information that may facilitate the development of strategies and agreements with organizations to support pediatric CKD care in Guatemala and other LMICs.

Materials and methods

A cross-sectional chart review and pharmacy survey was executed to assess the availability, access, and affordability of medications in patients at the Pediatric HD Unit of FUNDANIER. Records were reviewed from patients ranging from 6 to 18 years of age who received treatment in the unit during a 1-month period (February 2020). There were 30 patients at the HD unit at the time of the study. Patient charts were excluded if they had incomplete records, if they were transferred to other services during the month of study or if they had an acute kidney injury. Information collected included medication name, dose, frequency, dosage form, and route of administration. Demographic information was also collected to describe sex, age, and frequency of visits to the clinic.

Two pharmacies within the hospital perimeter, one public and one private, were consulted to determine generic and brand name drug prices. Generic medicines refers to drugs that are registered and used with the International Common Designation of the active ingredient and that demonstrates to be bioequivalent to the reference medication and brand name drug prices refer to pharmaceutical product that were first authorized for sale based on its documentation of effectiveness, safety and quality (Departamento de regulación y control de productos farmacéuticos y afines de la dirección general de regulación, vigilancia y control de la salud del ministerio de salud pública y asistencia social [DRPFA], 2023). Public pharmacy prices were identified via phone conversations with a pharmacy technician, while private pharmacy drug prices were identified via the internet. In the public pharmacy, a list of medication names was provided to the pharmacy technician who summarized the medication price information. For private pharmacies, most medications were identified via the pharmacy chain webpage. The chosen pharmacies meet the established requirements by the Ministry of Health, like the Health License and the products own a sanitary registration from Guatemala that indicates that the products meet de quality requirements to be marketed in the country.

Availability of medications listed on the website was not clear, thus study personnel called the medication home delivery service to confirm availability. All data was registered in a format that included information such as the active component, if it was brand name or generic, name, package quantity and the quantity that was needed to be acquired in order to complete a month's treatment (30 days).

Analysis

Availability of medications was confirmed (yes/no) as being in stock as reported by public or private pharmacy. Prices for generic and brand name medications were taken from private and public pharmacy public listings. Drug prices are summarized in US dollars (USD) using an exchange rate of Q7.70 Quetzales per 1 USD. We assessed affordability of medications first by identifying the cost of treatment for one month for each patient included in the study. Affordability was calculated by comparing the total treatment cost per month in relation to the minimum wage corresponding to an 8-hour work day in the non-agricultural sector (15), \$12.1 USD per day. The total treatment cost per patient was divided by the minimum salary per day to determine days' wage needed to cover treatment cost.

The International Medical Products Price Guide (Management Sciences for Health, 2016) was used to compare pharmacy prices in Guatemala to the international reference prices. The international reference prices used were the medians of the acquisition prices offered for the medicines to the suppliers of international agencies. In case the drugs didn't show the supplier price, the buyer price was used as reference. The Median Price Ratio was calculated for the drugs that were in the guide by using the following equation:

$$\text{Medicine Price Ratio (MPR)} = \frac{\text{median local unit price}}{\text{International reference unit price}}$$

The average and standard deviation of pharmacological treatment cost was obtained. "Total treatment cost" is reported as the average cost, across patients, for 30-days of treatment. The "total cost per patient" refers to the treatment cost without erythropoietin (EPO) and active vitamin D, as these medications are donated to the clinic and provided free of charge to patients.

The physical patient charts were reviewed and each information needed was registered in a database in Microsoft Excel. According to the dosage of each medication we obtained the total amount of tablets or syrup milliliters they needed to complete a month treatment, in that way we determined the quantity of medication they need to buy at the pharmacy.

Ethics

The protocol and study documents were reviewed and approved by the ad-hoc ethics committee at FUNDANIER in January 2020.

Results

Demographics

From 30 patients attending the HD unit at FUNDANIER, 22 patient records were included. Of 8 patient charts that were excluded, 7 were due to transfer out of FUNDANIER or moved to other programs such as peritoneal dialysis or kidney transplant, while 1 patient was diagnosed with Acute Kidney Injury associated to an autoimmune disease and his pharmacological therapy differed substantially from typical CKD patient seen at FUNDANIER, due to the fact that it included immunosuppressive drugs. Fifty-five percent of patients were male, 50% of patients were between 10-12 years old. Sixty-eight percent of patients came from areas outside of Guatemala City. Sixty-four percent of patients received HD treatment 3 times per week, and 36% just 2 times per week (Table 1).

Table 1. Demographic information

Variable	Hemodialysis Patients	N=22
Patients		
- Female	12	55%
- Male	10	45%
Average age		13 (*SD=2)
Type of vascular access		
- Catheter	14	64%
- Arteriovenous fistula	8	36%
HD Sessions per week		
- 3 sessions	14	64%
- 2 sessions	8	36%
Type of residence		
- Urban	7	32%
- Rural	15	68%

*SD:standard deviation

Pharmacological Treatment

Ninety-one percent of study patients had at least one antihypertensive agent including angiotensin converting enzyme inhibitors (ACE inhibitors) (82%) or calcium channel blockers (86%). Medications targeting calcium and phosphorus metabolism were documented in 96% of the patients, including Vitamin D (Alphacalcidol). Medications for anemia consisted of erythropoietin (EPO) by 100% of patients and iron by 45%. Some patients also used anticonvulsant medications (9%) and other nutritional support medications such as zinc.

Medication availability, cost

In the public pharmacy, 29% of generic medications, and 41% of brand name medications were available (total number of medications, n=18). In private pharmacies 94% of brand name medications, and 52% of generic drugs were available (n=18). Medications ranged in cost from lowest price medication folic acid (1USD, per month per 30 generic tablets, public pharmacy) to highest priced medication Amlodipine (127 USD, per month per 60 brand name tablets, private pharmacy). Brand name medications were higher priced at the private pharmacies in comparison to the public pharmacy. Amlodipine had the greatest difference in cost between brand and generic formulations when comparing between and among pharmacy categories.

Table 2. Monthly drug cost in dollars

Generic Name	Strength	Pharmaceutical form (units)	Private pharmacy		Public Pharmacy	
			Generic (USD)	Brand Name (USD)	Generic (USD)	Brand Name (USD)
Antihypertensives						
- Enalapril	10mg	Tablets (60)	32	40	2	21
- Amlodipine	10mg	Tablets (60)	61	127	3	36
- Hydralazine	50mg	Tablets (30)	--	38	--	--
- Doxazosin	4mg	Tablets (30)	48	60	--	--
- Doxazosin	2mg	Tablets (60)	68	--	--	--
- Carvedilol	12.5mg	Tablets (30)	25	35	--	19
- Carvedilol	6.25mg	Tablets (30)	16	32	--	--
- Atenolol	50mg	Tablets (30)	12	35	6	--
Drugs for calcium and phosphorus metabolism						
- Alfacalcidol	0.25mcg	SGC**(30)	--	51	--	15
- Calcium carbonate	750mg	Chewable tablets (90)	--	10	--	--
An ianemic Drugs						
- Erythropoietin*	2000IU	Injectable Sol.(1)	--	12	--	11
- Iron Sucrose	100mg/5ml	Injectable Sol.(1)	--	12	--	10
- Folic Acid	5mg	Tablets (30)	1	9	1	5
Anticonvulsants***						
- Valproic Acid	250mg/5ml	Oral suspension (480ml)	--	115	--	--
- Phenytoin	750mg/100ml	Oral suspension (480ml)	--	55	--	--
Others						
- Zinc	20mg	Tablets (30)	8	12	4	--
- Lactulose	65g/100ml	Oral Suspension (480ml)	--	76	--	--

Prices may vary according to the dosage prescribed to each patient. * Erythropoietin =price per unit, **SGC= Soft gel capsules, *** Anticonvulsants= the oral suspension presentation is equal to 120 ml, patients in average need 4 bottles per month which is equivalent to 480 ml.

Median Price Ratio (MPR)

The highest priced medication, amlodipine, was priced 88 times higher than the international listed price. Folic acid, the lowest cost medication, was 2 times higher than the international listed price. Enalapril and phenytoin were the only medications below the international reference Price (Table 3).

Table 3. Median Price Ratio (median local unit price/ International reference unit price)

Generic Name	Private Pharmacy		Public Pharmacy	
	Generic	Brand name	Generic	Brand Name
Antihypertensives				
- Enalapril	5	6	0.2	3
- Amlodipine	42	88	2	25
- Hydralazine	--	8	--	--
- Doxazosin 4 mg	20	25	--	--
- Carvedilol 12.5mg	27	37	--	20
- Carvedilol 6.25mg	23	44	--	--
- Atenolol	22	66	--	--
Drugs for calcium phosphorus metabolism				
- *Alphacalcidol	--	4	--	1
- * Erythropoietin	--	2	--	2
- Folic Acid	3	36	2	20
Anticonvulsants				
- **Phenytoin	--	2	--	0.2
- Valproic Acid	--	3	--	--
Others				
- Zinc	9	13	4	
- **Lactulose	--	8	--	--

*Alphacalcidol and Erythropoietin = price per unit.** Phenytoin and lactulose = price per 4 bottles equivalent to a month's treatment.

Pharmacological treatment cost

The average cost for a full month's treatment for brand name drugs acquired in private pharmacies was 495 USD versus 299 USD in the public pharmacy. The average cost for a full month's treatment for generic drugs was 414 USD in the private pharmacy, versus 239 USD in the public pharmacy (Table 4).

The program at FUNDANIER/Roosevelt Hospital provides two medications (erythropoietin and active vitamin D) to patients in the HD unit in order to help them decrease their pharmacological treatment cost. Total cost per patient shown in Table 4 is the average cost of the treatment without EPO and active vitamin D prices, that are provided by the program. Patients seen at FUNDANIER have total cost savings ranging from 176 USD to 295USD depending on generic/brand name medications purchased at public/private pharmacies (Table 4).

Table 4. Total pharmacological treatment cost per month in US dollars.
Cost is disaggregated by generic and brand name medications obtained in the private and public sector

	Generic		Brand name	
	Private Average (SD*) (USD)	Public Average (SD*)	Private Average (SD*)	Public Average (SD*)
Cost of medications with FUNDANIER clinic support**				
cost/month	131 (60)	63(53)	200 (94)	118 (71)
Cost of medications, with no clinic support				
cost/month	414 (86)	239(57)	495 (108)	299 (78)
Cost savings for patients seen at FUNDANIER				
cost/month	-283	-176	-295	-181

*SD: Standard Deviation. **refers to the treatment cost without EPO and Alphacalcidol as these medications are donated to the clinic and provided free of charge to patients.

Affordability

Affordability was calculated by comparing the total treatment cost per month with the minimum wage (Ministerio de Trabajo y Previsión Social, 2020). Drugs in private pharmacies for generic and brand name equivalents, were less affordable than drugs acquired in the public pharmacy. On average, monthly treatment with brand name drugs purchased in private pharmacies cost 41 days' wages, while the same purchase in public pharmacies, represented 25 days' wage. Generic drugs obtained in private pharmacies cost 34 days of work versus 20 for public pharmacies. This implies cost reduction between public and private pharmacies from 16 days for brand name medications, and 14 days for generic medications.

Table 5. Affordability of medication based on a monthly minimum wage in Guatemala

	Days' wages to pay for treatment				Days' wages to pay for treatment (with donations from clinic)			
	Private		Public		Private		Public	
	Generic	Brand name	Generic	Brand name	Generic	Brand name	Generic	Brand name
Average	34	41	20	25	11	17	5	8
Maximum	49	63	29	41	20	34	17	25
Minimum	19	26	10	14	1	1	1	1

* Days' wages including the price of the medications minus the monthly donation by the hospital (EPO and Alphacalcidol).

Discussion

This cross-sectional chart review and pharmacy survey provides evidence demonstrating the high cost of medications for patients receiving HD therapy in Guatemala. Monthly pharmacological treatment represents a cost of over 30 days' wages and represents a major barrier to obtaining treatment for children with renal disease (Vargas Copland, 2011).

There was a marked difference between the cost of medications in public and private pharmacies, as well as differences between the costs of generic and brand name medications. Multiple factors impact perceptions and consumer preference for generic medications as well as costs and access for these drugs. Guatemalan intellectual property law provides expansive protection for brand name pharmaceuticals resulting in significant delays for the introduction of generic medications into the market (Flood

et al., 2017). Lower procurement prices of generic medications to increase demand are likely the result of negative consumer perception of generic drugs in Guatemala (Cameron et al., 2011). Here, we show that 20 day's wages per month are needed for generic medications, versus 41 days for brand name medications in private drugstores. Generic medications are more affordable, but negative perceptions surrounding efficacy likely deter consumer acquisition of these products.

In the private pharmacy, more than 90% of brand name medicines for CKD were available were elevated in cost compared to reference prices. Regulation of drug prices supported by national policies in Guatemala and other similar countries may facilitate access to medications across the public and private health care sector (Anson et al., 2012; Acuerdo Ministerial N.º 276-2019). Implementation of coherent, evidence based pharmaceutical policies are important to ensure access to medicines for the population as a whole, such as the National Health Policy approved in 2019 but have yet to be implemented (Alvarez & Gonzalez, 2020). Medicines in private pharmacies were higher priced compared to international reference prices, which was also seen for medications in public pharmacies, although to a lesser extent. The impact of higher priced medication on a caregiver's wellbeing is apparent when considering the proportion of monthly income required to cover this cost and is a barrier to obtaining medication. Further, the overall impact on the wellbeing of patients and patient families (Anson et al., 2012) including life expectancy and general quality of life are at risk, and may be attributed, in part, to high priced medications that are rendered unattainable as a result of high cost.

FUNDANIER provides clinical care and social support, with the help of Roosevelt Hospital for key medications (erythropoietin and active vitamin D) to patients in the HD unit (Ramay et al., 2017). The monthly donation of medicines given to the patients is helpful in order to reduce days' wages spent on medications. For example, medication expenses may be reduced by 23 days' wages for patients who acquire generic medications in private pharmacies and reflects the positive impact and importance of donations for these patients.

This study provides insight on the importance of establishing policies to negotiate drug prices, also shows the importance, as a country, of establishing agreements with organizations to encourage development of legislation that ensures availability, affordability and access to medicines for all patients throughout the country.

The study has several limitations. First, pharmacy data was collected from a limited number of pharmacies but represent the most prominent pharmacies frequented by FUNDANIER patients. Pharmacies were not randomly selected which may impact the internal and external validity of the study. Also, not all medications included in FUNDANIER treatment schemes were listed on the international reference price list and was not possible to make a cross-country comparison with all the medicines listed. Medication prices are the result of input costs, tariff barriers, taxes, industry regulations etc. (Alvarez & Gonzalez, 2020), however, this study only compares prices among countries without exploring the cause. Finally, the study focuses on medication prices for HD patients, additional studies are need to describe medication costs for patients receiving other forms of KRT (Kidney Replacement Therapy) to determine the overall economic impact of medication cost in this patient population.

Limited access to generic medications, and overall high medication cost represent barriers to obtaining treatment for children with advanced renal disease. These challenges have the potential to impact treatment adherence and overall outcomes of advanced CKD pediatric patients. Extreme prices of medications provide a basis for implementation of stricter national pharmaceutical policies, thus guaranteeing medicine access to all populations. With the help of international organizations, Central American countries may make agreements with industries to provide medicines to patients at lower cost.

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