CHRONIC KIDNEY DISEASE IN NICARAGUA: A QUALITATIVE ANALYSIS OF SEMI-STRUCTURED INTERVIEWS WITH PHYSICIANS AND PHARMACISTS

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Independent report prepared by Boston University Research Team

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INTRODUCTION

Chronic Renal Insufficiency (CRI), more commonly referred to as Chronic Kidney Disease (CKD), is a serious and growing global health problem. The treatment of End-Stage Renal Disease (ESRD) involves dialysis or transplant, modalities which are currently not available in many parts of the world (Moeller, 2002; Bello, 2005; Levey, 2007). The major known risk factors for CKD, particularly in higher income countries, include diabetes, hypertension, cardiovascular disease and obesity (Lea, 2002; Ejerblad, 2006). However, in lower income countries common causes of CKD are often associated with chronic glomerulonephritis and interstitial nephritis, which are generally ascribed to infectious and parasitic agents (Soderland, 2010). Further, there are several localized epidemics or clusters of CKD, where dietary, occupational and environmental exposures have been hypothesized as causes. In Japan, exposure to cadmium contaminated food and water appears associated with renal tubular dysfunction and mortality (Nishijo, 2006; Kobayashi, 2009). Dietary exposure to a nephrotoxic plant alkaloid, aristolochic acid, was implicated in Balkan endemic nephropathy (Stefanovic, 2009); and food contamination by a mycotoxin, ochratoxin A, has been identified as causing an outbreak of CKD in Tunisia (Abid, 2003). In Sri Lanka, an epidemic of CKD of unknown causes among young male agricultural workers has been described elsewhere (Wanigasuriya, 2007).

In Central America, increased mortality due to kidney failure has been reported both in Nicaragua and El Salvador and may be particularly common among younger men and in certain regions of the Pacific coast (MINSA, 2009; MINSAL, 2010; Garcia-Trabanino, 2002; Cuadra, 2006). Published community prevalence studies in Nicaragua and El Salvador are consistent with the mortality data and have attempted to assess associations with pharmaceutical, environmental and occupational exposures (Torres, 2010; Sanoff, 2010; O'Donnell, 2011). However, to date, the causes of the apparently high prevalence of CKD remain unknown.

A team of researchers with Boston University have been working since 2009 in Western Nicaragua with the Chichigalpa Association for Life (ASOCHIVIDA), a local group of ex-sugar cane workers and/or their family members affected by CKD, and Nicaragua Sugar Estates Limited (NSEL), the largest sugar producer in Nicaragua, to determine possible reasons for the excess rate of CKD in this region (BU, 2010a). Through a contract with the Office of the Compliance Advisor/Ombudsman of the World Bank (CAO), we have conducted a number of research activities including: environmental testing, occupational assessment, biological testing, and piloting a cohort study, with participation and guidance by representatives of the workers and the company (BU, 2010b). In addition to our investigations focused on environmental and occupational exposures, we are interested in the possible contribution of pharmaceutical use and other medical conditions to CKD.

A number of medications are potentially nephrotoxic, including common non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxyn and diclofenac. NSAIDs are a known cause of kidney injury, particularly in the setting of volume depletion, pre-existing kidney disease or other nephrotoxins. Aminoglycoside antibiotics, broad-spectrum antibiotics requiring either intravenous or intramuscular administration, are also a well known cause of kidney failure, especially in patients with risk factors such as pre-existing kidney disease, concomitant nephrotoxic medications, advanced age, and dehydration/volume depletion (Schrier, 1999).

Personal communications with physicians and workers during field research in Nicaragua, and more recently results from a Pilot Cohort Study conducted in the same area, have identified a high occurrence of reported urinary tract infections (UTIs) among men, and a condition known among workers as "chistata." Chistata was described to our investigators as painful urination, and "kidney pain" or pain in the kidney areas (lower back). We also learned that certain beliefs regarding changes of hot and cold temperatures in the environment and/or in the body could be related to these conditions and the practice of water intake. Informal conversations with physicians and former sugar cane workers in Nicaragua suggested a lack of consensus among both physicians and pharmacists on the true frequency of UTIs, best diagnostic practices, and the prescription of NSAIDs and aminoglycoside antibiotics to treat UTIs or other medical conditions. This anecdotal information about UTIs and chistata raise questions regarding the meaning of a UTI diagnosis (typically not common among men), chistata, subsequent prescription of medications, and CKD.

To increase our understanding of health professionals´ perceptions regarding renal disease (affected population characteristics, causal hypotheses considered, symptoms, diagnostic tools, treatment and prognosis), as well as of the conditions mentioned above as potential contributors to CKD in Nicaragua, we conducted a series of qualitative interviews in Chinandega and Leon. Interviewees were physicians who are likely to diagnose or treat chistata, UTI and/or CKD, and pharmacists who are likely to fill prescriptions for medications or sell medications. The purpose of these exploratory interviews was to identify beliefs regarding the occurrence, diagnosis, treatment and prevention of chistata and UTI as well as practices related to the prescription and sale of medications with the aim to investigate whether further studies of a potential association between them are warranted, as well as explore other potential hypotheses regarding causes of CKD (e.g. use of herbal remedies).

METHODS

We sought to interview approximately equal numbers of physicians and retail pharmacists in the western region of Nicaragua (Leon and Chinandega), and anticipated that up to 10 interviews of each type of professional would be sufficient to help us identify themes and patterns in our findings. We used different semi-structured interview guides for physicians and pharmacists consisting of 34 and 24 open-ended questions, respectively (Appendix I). Interviews queried physicians and pharmacists for their opinions on the following topics: 1) prevalence and causes of CKD in Nicaragua; 2) most affected population; 3) availability and cost of diagnostic tests, medications and treatment for CKD; 4) beliefs regarding dysuria-related symptoms, prevalence of UTI and sexually transmitted infection (STI); 5) knowledge regarding indications for and nephrotoxic properties of medications (e.g., NSAIDs and aminoglycosides); and 6) perceptions of patients' practices regarding herbal remedies and visits to healers. Interviews also included a series of follow-up questions or probes, prepared in advance, in order to elicit additional information from the informant on these topics. Respondents were asked to provide clarification when the meaning of the original statement was ambiguous, or to expound on the point, present another story, or discuss feelings and impressions in greater detail. Prior to being finalized, a draft of the physician interview guide was tested with a physician in Nicaragua associated with our study team to determine if the length, organization and Spanish translation were appropriate.

In order to select individuals to be interviewed, we first acquired a list of public or government health care institutions from the regional Ministry of Health (SILAIS) and a registry of pharmacies in Chinandega and León. We also acquired a list of private health institutions or clinics, where renal patients in particular may get health care, from the Social Security System. Each of the two regions (Chinandega and Leon, respectively) contained one main referral hospital, 13 and 16 public health centers, 6 and 4 social security or private clinics, and 145 and 212 pharmacies. Although health centers often have pharmacists on site from whom patients get prescriptions filled (often for free and for the medications subsidized by the government), we chose to interview only pharmacists working at pharmacies that are independent of the clinics, where a greater variety of medications are available.

We sampled from the health care institutions to get a relatively equal representation of both geographical areas, rural and urban locations, public and private institutions, primary (health centers) and secondary (hospitals or specialized clinics) care facilities, and general practitioners and either nephrologists or internal medicine physicians. We selected pharmacies based on location in the same area as the sampled health care facilities (usually the one that was closest to the health facility). When multiple options existed, we chose those that were well-established, and/or had a large number of clients.

We contacted potential interviewees by telephone to request their participation. Informed consent was obtained prior to participant interviews. Ethical approval was obtained both from the Institutional Review Board of Boston University Medical Campus and the Ministry of Health of Nicaragua to interview up to 20 professionals. Interviews were conducted individually and in-person by a native Spanish speaker (ORR). All interviews were electronically recorded and then transcribed and translated into English by a professional transcription agency in the US. All

identifiers were removed from English and Spanish versions of the transcripts prior to analysis (MKS), and cross-checked for accuracy by the interviewing researcher.

Interviews were analyzed using standard social science methods for analyzing qualitative data (Patton, 2002). Each pharmacist transcript was assigned a letter (A-I), and each physician transcript a number (1-10). The transcribed text was coded to organize the interview content into categories relating to knowledge, experience, beliefs, and theories concerning exposures or medical conditions and CKD. An initial list of codes based on categories of questions used in the interviews was identified following a preliminary review of interview transcripts. Two analysts read through all of the interviews, coding the text separately and then meeting to review how codes were applied to the text. After initial coding, content analysis was conducted to analyze number of references to specific codes among interviewees (for example, "sun" was a code and each reference to "sun" in an interview with a physician was counted.) We separately analyzed the physicians and pharmacists before identifying similarities and differences between the populations. Information that might allude to the exact location of an interviewee or otherwise indicate the pharmacy or clinic has also been excluded from our results.

RESULTS

We completed 19 semi-structured interviews conducted in November 2010 with physicians (n=10) and retail pharmacists (n=9). Participation rate was 100% (i.e. no one refused to be interviewed). Interviews lasted on average 41 min (sd:11, min-max 29-70) and 18 min (sd: 4, min-max 14-25), for physicians and pharmacists respectively.

Table 1: Sociodemographic characteristics of interviewees.

	Physicians n=10	**Pharmacists n=9**
Sex		
Women	6	8
Men	4	1
Region		
Leon	5	5
Chinandega	5	4
Location		
Rural	6	6
Urban	4	3
Health Institution		
Health Center	7	NA
Hospital/2nd level health center	3	NA
Physician specialty		
General Practitioner	6	NA
Nephrologist/Internal Medicine	4	NA

Physicians had a median of 19 years clinical experience (range 9-30). Pharmacists had worked a median of 10 years in a pharmacy (range 1-25), six specified they had a degree in Pharmacy or Chemistry & Pharmacy, one was a primary school teacher and one had not finished the secondary education. In one of the rural municipalities where there was no pharmacy we interviewed the person in charge of a store or "pulperia", located very close to the health center and where we were told that many people go to buy antibiotics and analgesics sold over the counter.

Following, under bold headings, are the results of the interviews´ analysis. Physicians´ and pharmacists´ beliefs, experiences and practices are organized under several categories or topics, and presented as the interviewees referred to them (i.e. sometimes using literal quotes, sometimes summarizing them). These findings are presented without the opinions of the researchers, and without comparison of our findings to existing knowledge on the topics (which follow in the discussion section). Further, ***the views presented in the results section do not necessarily represent the current scientific understanding of the conditions or causal hypotheses***. The purpose of presenting results separate from the discussion is so that the opinions

and voices of those interviewed may be expressed to the extent possible, without bias or judgment of the analysts. Results concerning several topics (i.e. herbal medication and healers), that provided useful and important information, but that did not show a consistent relationship with CKD, are shown in Appendix II.

CKD[1]: A serious and growing problem in Nicaragua primarily affecting young men working as manual laborers

One of the first questions asked of all physicians and pharmacists is whether or not they think CKD is a problem in Nicaragua. All nine pharmacists and all 10 physicians stated that CKD is a problem or very serious problem, with one physician describing CKD in Nicaragua as a tragedy. Four physicians acknowledged its high association with death, with two referring to it as a major cause of death in their hospital (primary according to one, similar to heart attack according to the other). Six of the 10 physicians volunteered that they thought the problem was especially concentrated in the Western region of the country.

With the exception of one pharmacist, all pharmacists and physicians were of the opinion that the number of CKD cases each year has increased since they have been practicing medicine or working in a pharmacy, with one physician estimating that the number of cases has increased by up to 10-15% each year, and one pharmacist suggesting that cases have increased especially in the last five years: "In the last five years they've been dropping like flies, almost one person dead or very, very sick with this illness each day."

Four physicians suggested that the increase in cases may be associated with several factors related to diagnosis including increasing attention being paid to the epidemic and subsequent research and registries, clearer case definition, and improved laboratory facilities to make diagnoses (phys 2, 6, 8, 10).

All 10 physicians describe men as the most seriously affected population, with one suggesting a ratio of men to women of 5:1. Six of the nine pharmacists suggested more men than women are affected, with two suggesting men and women are equally affected, and one stating that the majority are women. Four of the physicians distinguished what they thought was a different etiology of CKD among women than men, suggesting that the majority of women who have CKD are more likely to also have known underlying risk factors for kidney disease:

> "There are women with kidney insufficiency, but that's for another reason. It could be diabetic nephropathy or arterial hypertension…" (Phys 3)

> "More men are affected than women… This doesn't mean that women are not... but these are women who have a chronic pathology to begin with." (Phys 10)

[1] In Spanish we are using the acronym IRC (CRI in English) instead of ERC (CKD in English) in the results section. The "I" stands for "Insufficiency" instead of "Disease". CRI is how the disease is most commonly known in the area, and the word used during the interviews by the interviewees and the interviewer. Interestingly, as exposed further in the report, the "I" stands both for "Insufficiency" and "Infection".

A similar distinction regarding etiology of disease was made by physicians when referring to the age of the affected population. Seven of 10 physicians describe the affected population as young (less than 45 years of age) and, of these physicians, several noted the lack of traditional risk factors of hypertension or diabetes:

> "There are both young and old people, but it strikes me that there are many young males… for example, this year we had a patient that died. He was really young, 27 years old. In a previous year we had a patient who was 21 years old. When we discovered the disease he was already in stage 5, terminal." (Phys 10)

> "What caught my attention was that there are young people, very young, and that they are rapidly getting worse. We have them age 20, 23, 24, and I am telling you we have detected it in people that maybe have two years, and they have deteriorated, significant health deterioration…" (Phys 8)

Two physicians said that CKD affects primarily older men, more than 45 or 50 years. However, one of these physicians (Phys 4) explained that about 10-15% of his case load is younger patients "ages 20 or 22" and they are "the ones in which the cause is almost totally unknown in our area." Four of the nine pharmacists said that young people are most affected, two pharmacists suggested that older people are most affected and at greater risk, and one said that CKD affects people of all ages.

Overall, physicians and pharmacists expressed uncertainty when asked if CKD presents in higher frequency within families. Only one physician was certain that CKD affected cousins and siblings, and felt that the etiology of CKD was not explained by shared environmental or occupational exposures. However, another physician described actively looking for but not finding any examples of CKD in families. Yet another physician did acknowledge seeing families where many members died from CKD, but noted that they were mostly agricultural workers and expressed uncertainty as to whether cases are due to shared occupation, or a family susceptibility (aside from diabetes or hypertension). While some of the physicians knew of similar cases of families severely affected, most did not think they had sufficient evidence to conclude that CKD is clustered in families. Similarly, the majority of pharmacists thought CKD may occur in families, but not for hereditary reasons: "It happens in families. At the beginning it was thought to be hereditary. It may be that they are exposed to the same things" (Pharm H). Two pharmacists thought CKD was hereditary and two did not believe CKD occurs in families at all.

We asked about racial or ethnic patterns of disease, and, on the whole, physicians and pharmacists said there are no differences in CKD by race or ethnicity because the population is relatively homogenous and mixed, or "mestizo." Only Phys 10 suggested that he sees it more in "mixed/mestizos" or "dark" people than "white" people.

Seven of the 10 physicians identified agricultural workers, or people who work in fields and ingenios, as those being most affected by CKD: "What I am certain of is that it happens more in people who work in agricultural areas, we are sure of that" (Phys 1). Similarly, eight of nine pharmacists thought there was an occupational association, with one pharmacist extending

the observation to people who live in rural areas, distinguishing their CKD from the CKD that results from preexisting diabetes or hypertension:

> "Those who are not diabetic are almost all males who work in the fields…. The most affected ones are, well, from the rural counties who work with pesticides and insecticides…. And then there are those from the city who are diabetic." (Pharm D)

Field workers and types of agricultural worker mentioned by physicians and pharmacists included fruit pickers generally, and workers on banana, cotton, melon, peanut, rice, and sugar plantations. One physician addressed the widely held impression that it was a disease of sugarcane workers suggesting that perception is no longer the most popular: "…now people are a little more aware that it's a health care problem that can affect anyone at any age." However, this same physician was among those who believe that the people most affected are those who work in the fields. One pharmacist (Pharm H) and two physicians (Phys 4, 10), two of the three who are located in an area where mining is a common occupation, mentioned mine workers. Of them, one physician suggested that the majority of miners are seen by physicians who are part of the company health care plan, so that physician was unlikely to treat them.

Other occupations identified as being most affected include construction workers and bricklayers. Pharm G expressed the least certainty about occupational association with CKD, at first stating that people who work "heavier jobs" are more affected, but then saying there are CKD cases who work light jobs, so it is "a little bit of everything."

CKD symptoms, diagnosis, prognosis and treatment[2] by physicians

Three of the physicians remarked that by the time patients come to see them; they are in advanced stages of disease (Phys 1, 2, 8). However, when asked about signs and symptoms of CKD patients, all physicians agreed that patients are asymptomatic at the beginning or with non-specific symptoms such as irritation, arthralgias, myalgias, cramps, nauseas, loss of appetite, paleness, tiredness, and headaches (due to elevated blood pressure). One physician mentioned anemia as "almost always" giving him a clue to the occurrence of CKD, and two were very clear that hypertension occurs as a consequence of CKD and not a pre-condition.

Seven of the 10 physicians said that patients would have no or very little proteinuria[3]. One of them provided the example of just one or at most two crosses in the dipstick (Phys 8). Physician 5 mentioned urinary tract infections as a potential problem presented by a CKD patient early on, and another physician repeatedly suggested that heat strokes are likely to result in CKD:

[2] For a detailed summary of drugs that physicians said they use to treat CKD, see Appendix II.

[3] The type of CKD presumed in the area among young males is tubulo-interstitial. A marked preteinuria is not expected in this type of chronic renal disease.

> "Normally, they don't present symptoms [of CKD], but the symptoms that they do present with when they arrive for the first time, are generally heat strokes, people are working and have cramps, nausea, vomiting, with fever. …After re-hydrating them, people improve and the creatinine levels after three or four months can lower from 2.8 or 3, to normal ranges. And they get reintegrated to work, but they still suffer from heat strokes. So there are possible consequences from dehydration." (Phys 1)

When asked on what tests do they rely on for making diagnoses of CKD, all physicians responded that the observation of decreased renal function over time would be the basis for the CKD diagnosis. Four rely on a formula to estimate the glomerular filtration rate. Five instead rely on a serum creatinine cut-off point (between 1.2 and 2.4mg/dl). Creatinine tests, however, were not available at one of the health centers. Other accompanying diagnostic tests mentioned are a complete blood count, glycemia, uric acid and a urine analysis. Also mentioned by physicians interviewed at hospitals were the 24 hour urine and blood urea nitrogen (BUN) tests.

Seven of the physicians would also want to have kidney ultrasound, to look for evidence of decreased size and hyperechogenicity, though physicians at the health centers would need to refer the patient to a hospital or advise them to get the ultrasound in a private clinic (hospitals and specialized centers had ultrasound equipment). In his answer about diagnosis of CKD, one physician responded using the words chronic kidney *infections*:

> "[With the general urine exam] we can have data that give us signals of a chronic kidney infection, just starting or advanced. CKD signs will be changes in the cylinders, a change in urine density; we can find a change in the pH, within the important phases, and the leukocyturias, that don't have an established etiologic cause. That should get our attention and start us to investigate." (Phys 5)

When asked about standards for diagnosis and treatment of CKD, seven of the ten physicians said they do not have access to national or regional CKD protocols or guidelines. Two physicians said they use national guidelines for other chronic diseases such as hypertension or diabetes to guide the diagnosis and treatment CKD. Two said they ground their practice in their own experience and familiarity with CKD (i.e., what they learned during their training and by reading the literature), and one physician referred to an "ad hoc" protocol developed by a consensus of local physicians. One physician acknowledged that there has been little training on diagnosis and treatment of CKD:

> "They only call us to get training when it is about health care of women, children and other illnesses in the area, mainly communicable diseases. But…hardly anything about [CKD]. We have had very little training." (Phys 6)

The remaining three physicians who claimed to have access to CKD-specific diagnosis and treatment guidelines referred to Nicaragua's Nephrology Association protocol, Ministry of Health protocol, and International standards published by the National (US) Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI).

Regarding survival rate of CKD patients, there was tremendous variation in reports of how long people live once diagnosed with CKD, from months to 10 years, with one physician saying it could be 15 years if they get help. Across the board, physicians suggested that survival largely depends on stage of diagnosis, self-care and behavior (nutrition), and access to treatment. Two physicians (5 and 6) refer to family support as a key determinant:

> "If we had family support… they are very cooperative, but they're people of few resources, they become like a burden for their family, and many of them are also patients who are alone, they're not retired, they're in poverty, so really, that kind of speeds up the suffering." (Phys 5)

Two physicians refer to reasons why patients choose not to go on dialysis. Phys 2 suggests that people do not begin dialysis because they do not understand it: "People do not accept the procedure. They have incorrect ideas about the treatment and think they will die sooner." Phys 4 elaborates suggesting that many patients don't accept dialysis possibly for cultural reasons having to do with the peritoneal catheter:

> "…or due to the fact that some don't have home conditions, others live outside of the city, access to a means of transport is very inaccessible, it's very inadequate. So then they don't accept these methods and they pass away. Definitely in a short period of time. Maybe in months. The majority of patients who aren't on hemodialysis therapy or peritoneal dialysis, pass away in a short period of time, due to the complications from the renal disease itself, without adequate therapy."

Potentially contributing to the belief that people die sooner on dialysis, Phys 5 explained that people who go on dialysis do tend to die sooner, but explains that the reason is that they are diagnosed very late, and their CKD is so advanced when they begin dialysis.

Causes of CKD? Strong sun, hard work, and… water?

Nine of 10 physicians identified occupation, or specifically exposures at work, as a likely cause of CKD. Six of the 10 physicians used the term "multi-factorial," while describing the cause of CKD, with the remaining four listing a variety of possible contributing factors. Sun and heat exposure at work rather than any specific occupation was the major perceived occupational factor associated with CKD, with seven of 10 physicians referring specifically to work under the sun:

> "Patients have worked in agriculture - more than anything they have been exposed to the sun a lot, they have been exposed to dehydration, they work with sugar cane, they work in the cotton fields." (Phys 6)

> "The majority are young men who have worked under the sun, under the heat, and maybe they haven't been drinking enough liquid when they have sunstroke or dehydration." (Phys 7)

Chemicals used in agriculture that result in potential exposures to worker and the community at-large were described as a possible cause by half the physicians. Phys 4, however, made a point of suggesting that chemicals were not the likely factor among occupational exposures. When referring to the higher incidence among men, Phys 4 stated:

> "Men have other factors associated with deterioration of kidney function… the use and abuse of substances, alcohol or drugs, strenuous exercise or work, not necessarily exposure to pesticides, but work in the fields, or work in areas with many hours exposed to the sun…"

Three physicians talked about lack of access to clean drinking water, with two referring specifically to heavy metals in water. Phys 8 suggested drinking water stored in metal tanks may leach heavy metals (lead and iron) into the water.

Pharmacists overall had less nuanced responses regarding the causes of CKD than the physicians. While water was the common denominator in 8 of 9 pharmacist responses, there were two distinct perspectives on the role of water in CKD. Four pharmacists very clearly believed that not drinking *enough water* was the primary problem, while four pharmacists believed that drinking *contaminated water* was the problem.

Three of the four pharmacists who thought dehydration was the primary cause of CKD also thought it was not the only cause, or else "everyone would be dead," according to Pharm B:

> "They are sunburned, they don't eat well… I think that [CKD] is from the dehydration they get in the fields, their work is hard, hard, and they ruin themselves taking diuretics and further draining their body water."

Of the four pharmacists who identified contaminated drinking water as the primary cause of CKD, three mentioned particular contaminants as pesticides, one mentioned volcanic ash, and one industrial exposures generally. Only one pharmacist, from the city, suggested that pesticides and "overall quality of life" are the cause of CKD among farm workers.

More than half of the physicians made the point that the causes of the CKD epidemic in the Western region of Nicaragua did *not* include the traditional risk factors of diabetes or hypertension. As Phys 2 stated, "I know that diabetes is the main cause of kidney insufficiency everywhere, except [here]." Five physicians volunteered estimates of the ratio of CKD cases caused by these risk factors to CKD cases of unknown etiology. These estimates range from half of the cases to 10 percent.

Four physicians suggested that use of nephrotoxic medications might be a cause of CKD. Physician 2 referred to abuse of medications by patients: "Gentamicin, for example… people use this a lot. So, I do think this is highly connected to [CKD]." Phys 1 said they see a lot of lupus and arthritis for which patients often take antibiotics and NSAIDS, which he believes, can be related to kidney lesions. Phys 7 made the association between CKD and UTIs, referring to the nephrotoxic properties of the antibiotics prescribed to treat the repeated UTIs. Two other

physicians also made the connection between CKD and diagnoses of other conditions including UTI and chistata (see more in following sections).

Three physicians identified alcohol as contributing to CKD, and one physician also identified poor nutrition. And two physicians suggested that an underlying or previous chronic illness, other than diabetes or hypertension, might be a causal factor. Phys 4 believed that the CKD might be a post-infectious glomerulonephritis that resulted in kidney damage early in life or an immunological pathology. Phys 10 proposed that obstructive pathology and renal calculi or kidney stones might explain 20% of the cases in men. He also specifically mentioned leptospira as a frequent infection possibly related to CKD:

> "Well, now we have leptospira, which means renal damage and it is also a public health problem. We had patients admitted here with abnormal creatinine, with confirmed diagnosis of leptospira. That is frequent."

Regardless of the precise cause or causes, both Physicians 1 and 2 offered the opinion that the disease almost certainly involves an interstitial damage of the kidney:

> "Biopsies have shown an interstitial nephritis with different immunologic markers. Sometimes you have C3, sometimes immunoglobulin IgM. But no, let's say that either one or the other defines you. And generally, there's more interstitial damage, with less glomerular lesion." (Phys 1)

> "I insist that I believe there is an interstitial nephritis, caused by something in the environment that we have been unable to determine." (Phys 2)

Further complications: "Chistata" and UTI

When asked about the condition "Chistata," all physicians agreed that chistata is a colloquial term used to characterize a constellation of symptoms including "pain," "burning" and the "urgent" need to urinate, with chistata approximating the clinical term dysuria. Although dysuria may be a symptom of UTI, STIs[4], and kidney stones, or, far less commonly, malignancies of the urinary system (i.e., bladder or prostate cancer), physician opinions varied as to the relationship between the set of symptoms known as chistata and the diagnosis of UTI.

All but one physician said that dehydration is a probable cause of chistata, with all but two physicians also saying that UTIs are a cause of chistata. In summary, seven of 10 physicians said that the symptoms known commonly as chistata can be caused by both dehydration and UTIs.

[4] We do not include discussion of STIs in our findings due to the fact that none of the physicians, and 8 out of 9 pharmacists, thought STIs are unrelated to the CKD epidemic in the area. One physician discussed a relationship between chistata and STIs but thought that only kidney infections could play a role in the CKD epidemic. One pharmacist suggested that untreated STIs (as well as UTIs, which we discuss) could lead to CKD.

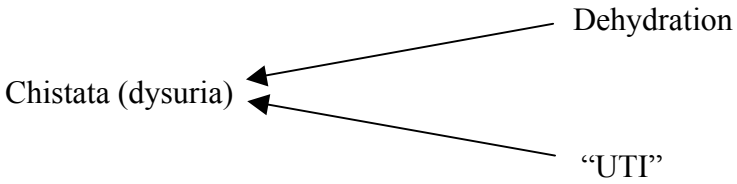

Figure 1. Perceived possible causes of chistata by physicians

There was disagreement among physicians, however, as to how closely infection was related to chistata, with some physicians equating the two, and at least one insisting that sometimes in the presence of chistata, lab tests do not confirm a UTI, and therefore "they cannot just be considered synonymous."

When queried further about UTI, four of the ten physicians claimed to diagnose UTI based on the results of a urine culture. However, two of these physicians acknowledged that they do not have the facilities to analyze a urine culture and, as one stated, it would be "at the cost of the patient." Instead, these two along with five others admit to diagnosing UTI based on a general urine exam indicating the presence of leukocytes, bacteriuria, and/or nitrites. In most instances these physicians acknowledged that a urine culture would be ideal, but not possible. One such physician suggested that with present diagnostic methods, physicians are probably over diagnosing UTIs:

> "What happens is that we have been doing a bad management of the urinary tract infections. What happens is that sometimes we consider that the appearance of white blood cells, leucocytes, in urine is enough. But it is not like that." (Phys 9)

When asked about the relationship, or possible association, among chistata, UTI and CKD, seven physicians said that UTIs may be associated with CKD, with two physicians suggesting this would be true only of patients with upper urinary tract infections such as chronic pyelonephritis. Five physicians thought the connection between UTI and CKD had to do with repeated, non-treated or inadequately treated UTIs associated with regular use of broad spectrum antibiotics, increasing antibiotic resistance, and failure of treatment adherence. Of these five, one physician (Phys 7) specifically attributed the connection between UTI and CKD to the nephrotoxic properties of the antibiotics prescribed to treat the repeated UTIs.

Medications for treatment of UTI and Chistata by physicians

When asked how chistata is treated, seven physicians stated that they recommend oral rehydration solutions and increased intake of liquids, and seven physicians recommended urinary analgesics such as phenazopyridine (Pyridium®) or the antibiotic nitrofurantoin as the first remedy or relief for pain and burning urination. Five physicians specified that they would not treat with anything else without further tests including urinalysis. Two physicians at hospitals said they would also do a urine culture, and two said they would request an ultrasound. All five who said they required further testing then enumerated a list of antibiotics that they might prescribe, including fluoroquinolones, amoxicillin, and penicillin, with only one (Phys 10) naming aminoglycosides: "But… we have to be very careful with kidney patients, with the previous levels of creatinine, because gentamicin is nephrotoxic."

Treatment of UTIs includes the same urinary analgesics and antibiotics enumerated for chistata plus other beta-lactam antibiotics (Ampicillin/sulbactam), and cephalosporins like cephalexin, cefixime, and cefadroxil. Again, gentamicin was recalled by one other physician to be used in very select cases, cautioning of its nephrotoxicity. When answering a specific question regarding the uses of gentamicin later on in the interview, most physicians agreed that it was reserved for severe UTI or sepsis patients with no oral medication tolerance usually in the hospital or admitted at the health center beds. In such cases, gentamicin is administered via intramuscular or intravenous. Four physicians said they would use gentamicin only if a urine culture or antibiogram were used for diagnosis. Two physicians noted the nephrotoxicity of this antibiotic when referring to treatment of UTI with one saying that for this reason he would not use it at all, in addition to concerns about genatmicin-resistant strain of bacteria. One physician noted they have to use it sometimes due to the fact that they don't have many options to choose from.

Regarding NSAIDs, eight physicians acknowledged the possible nephrotoxic effects of long-term intake of NSAIDs. Of them, six would not prescribe them (or would restrict their use) in CKD patients. Phys 1 said he tries not to use them, instead prescribing paracetamol, metamizol or tramadol. Two physicians said NSAIDS are prescribed for back pain with one suggesting the pain may be associated with UTI (Phys 8).

Pharmacist perceptions of UTI, Chistata, CKD and their treatment

Pharmacists did not make the same distinctions that physicians did among chistata, UTI, and CKD. Complaints of back or kidney pain, and patients with chistata, UTIs and CKD were largely considered by pharmacists to be in the same group with no clear boundary between them. In fact, three pharmacists referred to CKD as an infection in response to the first question about whether CKD is a problem in Nicaragua: "It is [a problem] here, yes. There is a lot here. For example, in my family I have an aunt and her three children who have died of infection" (Pharm D).

When asked specifically whether chistata, UTIs or STIs were related to CKD, all nine pharmacists were of the opinion that UTIs and chistata are related to CKD. Three pharmacists said UTI and chistata are like the first step, or "warning," of CKD. Three other pharmacists suggested CKD results from UTIs that were not treated or did not receive the correct treatment (D, F, I). In response to a question about the causes of chistata, specifically, Pharm F responded in a manner representative of many pharmacist opinions: "Chistata is the mild form of kidney problems or infections that advance the lowering of creatinine." This same pharmacist also said that chistata is a frequent symptom of CKD patients: "they, those who have CRI, are also very much affected by chistata."

Range of kidney problems

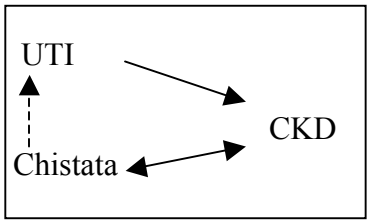

Fig 2. Temporal evolution of symptoms and disease. (by pharmacists)

Pharmacists described symptoms of patients who come to them with CKD, with eight of the nine describing symptoms of chistata (back pain and burning while urinating), and four included the words "fever" or "infection" in their description: "Trouble urinating, pain in their back, fever. In certain cases where the infection is very severe there is sometimes vomiting." (Pharm G) Pharmacist B further described the symptoms of someone with advanced kidney disease:

> "Well, I see dehydration, with faces like [scrunched up], uncomfortable. When they have had the illness for a while and are deteriorating, they look yellow, thin. There are others that swell. When cases like this come in, I send them to the health center to get a doctor."

When asked specifically about prescriptions for CKD filled by pharmacists, eight of nine pharmacists named the urinary analgesic phenazopyridine, in addition to antibiotics including norfloxacin, ciprofloxacin, cefadroxil, cephalexin, cefixime, gentamicin, amikacin, azithromycin, and trimethoprim-sulfamethoxazole. Other medications included one mention of iron for anemia, and calcium (Pharm D), and enalapril (an ACE inhibitor). One pharmacist described common CKD prescriptions as such:

> "For kidney insufficiency, doctors from health centers here commonly prescribe ampoules called Gentamicin, Trimethoprim-sulfa; this is what they commonly prescribe." (Pharm F)

Pharmacist F was one of two pharmacists who admitted to selling antibiotics without a doctor's prescription. Two additional pharmacists described difficult situations where patients demanded a diagnosis from the pharmacists, or that they be given a specific drug:

> "Here people say, 'sell me something for chistata', the majority want you to sell them furosemide pills. These pills dehydrate them. It's my duty to explain to them that this pill is not for that. 'Take the fenazopridine (phenazopyridine) for that.' 'No because that stains me (the urine), give me the half white ones please… look, give me the white ones, if not I'll go shop somewhere else'." (Pharm B)

Pharmacist B also explained that when people have a diagnosis they can get treatment at the health center, but before a diagnosis they go to the pharmacy. Three of the four pharmacists who described pressures of selling medications without prescriptions also observed what they thought was poor adherence to treatment by patients.

For the most part, pharmacists described filling the same medications as the physicians for treatment of chistata, UTIs and lower back or kidney pain (i.e., antibiotics). Pharmacists did not mention or discuss oral rehydration solutions. Seven pharmacists (A, B, C, D, G, H, I) said they would treat chistata with the urinary analgesic Phenazopyridine (Pyridium® or Urogesic®). Five pharmacists named antibiotics: nalidixic acid or Wintomylon® (pharm A, B) nitrofurantoine or Uvamin® (pharm C), trimethoprim (Pharm F) , and pharmacist I, who said antibiotics in general. Three pharmacists (E, F, G) said that they would first recommend diuretics such as furosemide with Pharm F stating, "Furosemide is the most common, I sell it every day." Recognizing that diuretics could have the effect of further taxing the kidney, Pharm E explained: "When I sell it, I tell people to drink plenty of fluids. But at the end, that is the decision of people, right? But I let them know that [the medication] can damage the kidney."

As pharmacists suggested that the conditions of chistata, UTI, and CKD are manifestations of a shared problem at different ends of a spectrum, similarly, their recommendations of treatment for each included basically the same battery of antibiotics. When asked specifically how are UTIs treated, seven pharmacists (B, D, E, F, G, H, I) said with antibiotics that included: nitrofurantoin, quinolones (ciprofloxacin, norfloxacin), amoxicillin, trimethroprim- sulfamethoxazole, cephalosporins (such as cefadroxil, cefaloxin), and aminoglycosides such as amikacin. Three pharmacists said the treatment for UTIs would be the same for chistata (Pharmacists B, C, I), which included both phenazopyridine and antibiotics. However reiterating pressure from patients to self-prescribe, Pharm B added:

> "I try not to, because it is bad to just give antibiotics to the people. But for whatever pain, the people want to take antibiotics. It is a bad habit that we have in this area."

When posed with the question, "What would you do if a person with lower back, or flank pain, came to you asking for help?" responses revealed the range of opinions and practices regarding the role of pharmacists in the diagnosis and treatment process. On one end of the spectrum are those who said they would not prescribe them anything until they are diagnosed by a physician (Pharm C), to those willing to directly provide treatment (Pharm F). Most said they would first recommend the patient obtain a urinalysis and have it interpreted by a physician, while, in some cases, the pharmacists offered to interpret lab results themselves. Treatments included phenazopyridine and antibiotics such as cefadroxil, ciprofloxacin, norfloxacin, levofloxacin, trimethoprim-sulfa, azithromycin; antispasmodic drugs such as Rilaten®, Spasmocin® or Sertal®. Two pharmacists also said that they could also recommend, in the context of back pain, analgesics (Pharm G) or more specifically ibuprofen (Pharm E). Once more another pharmacist described the pressure to sell antibiotics over the counter with no diagnosis at all:

> "First I ask if I can give them something for the pain, but here the people, in Nicaragua, like to get treatment in the pharmacy, so they'll say, 'Why can't you give me one directly? Why do I have to go and spend money to get an exam?' So I recommend them a treatment, like cefadroxil." (Pharm A)

Physicians' perception of pharmacists enabling self-medicating patients

As previously noted, four physicians suggested that self-medication, or over the counter sales of potentially harmful medications, could be contributing to CKD. Physician 3 named the use of NSAIDs and aminoglycosides as likely causes in the multifactoral etiology of CKD. When discussing patient complaints of back or kidney pain, Physician 2 stated that "overuse of painkillers and antibiotics are contributing to the high incidence of CKD". Further in the interview, this same physician said that "the problem is that NSAIDs and gentamicin are sold in the markets of cities like candies" and that "agricultural workers with back pain get shots of gentamicin by vendors in stores."

Physicians 1 and 9 emphasized how some patients insist on taking diuretics for chistata even when the physician tries to convince them it is not a good idea:

> "They come saying, 'I didn't drink water today, I'm sure I'll get chistata, in about two or three hours.' … these patients that normally have chistata are dehydrated most of the time, so what they do is take a furosemide to get rid of it. And later, they arrive with cramps, more dehydrated, and it becomes chaos." (Phys 1)

Kidney stones: In or out of the equation?

Regarding kidney stones, there was not agreement in responses among pharmacists or physicians. Four pharmacists said kidney stones were not common (Pharm B, C, D, F), while the other four pharmacists (Pharm E, G, H, I) said they occurred very frequently in the community. One even said that stones were also common in the gallbladder (Pharm E). Pharmacist H named "kidney stones" as another possible cause of chistata.

Similarly, four of the physicians said kidney stones were not very frequent (1, 3, 4, 9), with Phys 3 saying that they are, though, more frequent in sugar cane workers. Both physicians 1 and 3 offered a figure: 3% of patients coming to consult. While six physicians (Phys 2, 5, 7, 8, 10) said kidney stones were very frequent:

> "Yesterday for example, I was on call and there were six patients with nephritic colics that were under observation in the emergency room. In fact, one of the doctors was suffering from a nephritic colic. So it is common." (Phys 2)

> "Many people get kidney stones or "sand". Many of those who get an ultrasound show this. The urine test shows plenty of calcium oxalate." (Phys 8)

Again, one physician suggested that the occurrence of kidney stones "has nothing to do with CKD patients" (Phys 2), with another (Phys 5) stating, "Nephrolithiasis has a lot to do with CKD" and Phys 10 proposing that 20% of the CKD cases could be explained by obstructive pathology or kidney stones.

Three physicians (Phys 2, 4, 8) named kidney calculi as a possible cause of chistata in the area, with two of them linking that with "too concentrated urine" or "sandy urine" due to dehydration. One physician (6) said that of those patients coming with a UTI that could have an

ultrasound being made, two or three out of 10 would show kidney stones, and that this fact was more frequent in males.

Hydration and changes in temperature

We asked all physicians the following question: "We have heard from people who work in sugarcane that changes in temperature (from hot to cold) may be dangerous. For example, drinking cold water when hot, or having a shower after a long day of hot work? In your opinion, are any negative health outcomes likely to result from this type of behavior?"

All 10 physicians seemed to be familiar with the notion that a rapid change in temperature is believed to cause health problems, with varying opinions of whether this is true. Three physicians (3, 6, 10) referred to respiratory problems, cough and cold likely to result from abrupt change in temperature. However, Phys 10 talked only about abrupt temperature changes in the environment (i.e., very hot weather suddenly turns cold), aggravating asthmatic patients or individuals with COPD, not behaviors that would result in a person's body temperature changing rapidly. Physicians 3 and 6 were not as specific, and said if any harm would come from a change in temperature, it would most likely be respiratory. Phys 3 suggested the belief that one would get a bad cough or cold after being in the sun and then bathing "depends on the cultural and economic situation of each person." Phys 9 similarly summed up the notion that ill health comes of temperature change to culture: "[The belief] doesn't have anything to do with anything. It's the culture of a person." Phys 4 referred to the belief as "a myth among the population."

Three physicians (2, 6, 9) referred to the belief that sexually transmitted infections come from bathing:

> "There are actually people that believe that gonorrhea is contracted that way. There are people that tell you, 'After I worked all day long, I took a shower and that is why I got the disease.' People think that sexually transmitted diseases are related to these abrupt temperature changes." (Phys 2)

Physicians 6 and 9 referred to the commonly used saying that to "pass the river" refers to the act of bathing, and then acquiring an STI. This belief may be why four of the 10 physicians focused on the part of the question that asked about bathing (Phys 1, 2, 3, 6,) rather than drinking water. Phys 1 referred to the belief that bathing after a long day may be associated with muscle and joint pains, which he thought was a reasonable concern among workers. Only one physician (Phys 7) talked about the consequence of drinking cold water when hot, saying that no harm would come except perhaps the painful sensation of the cold water on the throat.

Two physicians talked about abrupt changes in temperature resulting in facial paralysis (Phys 5 and 8). Phys 5 really did not answer the question, talking instead about cases of heat stroke and resulting facial paralysis. Phys 8, however, talked at length about the belief that change in temperature can result in facial paralysis:

> "We handle it more scientifically. Logically, sudden temperature changes can cause problems. For example, you do not need to have a serious trauma to cause a

> partial paralysis... Sometimes a sudden change in temperature, when you're hot and get a very cold wave, which is a trauma, a trauma of skin temperature change. …there are many people with partial paralysis. …for example, people have come here, some older women who may have their little stores and say, 'Look, I only went to sell some ice and I had just stood up, but not to sell. I went to the refrigerator. I opened it and then felt pain on the face. And then it looked like my face had gone sideways.' So traumatic facial paralysis by the sudden temperature change, they say."

Although pharmacists were not asked about their beliefs regarding change in temperature, Pharm B offered that chistata may be caused by dehydration and… "Also a quick change in temperature, maybe when hot quickly turns cold; you take off your shoes. That can also affect it."

Last word

At the end of each interview, when asked if there were anything the interviewees would like to add, one physician identified the need for psychological help among CKD patients suggesting a social worker conduct home visits. Recognizing that a social worker will not bring "suitcases full of money to resolve their problems," Phys 8 suggested that a social worker may "be a sign of hope" and help a patient "handle this disease in a better way." Pharmacist E responded saying he would like more information and training: "I would really like to know more in order to help people." Another pharmacist wanted to say that CKD is a social issue that demands the action of several government institutions, including the highest executive level, and in particular because when workers are diagnosed with CKD, they are no longer given employment.

DISCUSSION

Interviews of physicians and pharmacists working in Western Nicaragua corroborated the existence of an epidemic of CKD. Characteristics of the epidemic as described by the physicians and pharmacists are consistent with results of community prevalence studies in the region (i.e., more prevalent among men than women, starting in young ages, and associated with occupations, mainly agricultural work involving different crops but also mention of miners and construction workers) (Torres, 2010; Sanoff, 2010; O'Donnell, 2011). The lack of ability of diabetes and hypertension to explain the CKD epidemic in Nicaragua was also highlighted by the interviews.

The interviews provided useful insight on some of the hypotheses to-date regarding the etiology of the CKD epidemic in Nicaragua and the Central American region. Most of the physicians noted that proteinuria would not be expected among this CKD of unknown causes, corroborating observations of infrequent and mostly low grade proteinuria among CKD cases in the region (Garcia-Trabanino R, 2005; Torres, 2010; O'Donnell, 2011; Orantes, 2011). This evidence is compatible with a tubule-interstitial damage rather than glomerular. Exposures to agrichemicals, heavy metals, alcohol consumption, and infectious diseases, all speculated causal hypotheses in the area, were also mentioned in the interviews. Nevertheless, the primary hypothesis to emerge from the interviews relates to the role of heat stress, involving exposure to hot sun, physical work and dehydration.

Both physicians and pharmacists regarded occupational and environmental exposure to sun and heat as critical factors associated with the occurrence of CKD. This corroborates published data from Nicaragua (Torres, 2010) indicating that CKD may be higher among occupations in which strenuous work happens at high temperatures (e.g. sugar cane workers, miners, etc), conditions that would predispose workers to volume depletion and muscle damage. Several community studies have consistently found higher CKD sero-prevalence associated with low altitude as a proxy of exposure to higher temperatures (Laux, 2011; Torres, 2010; O'Donnell, 2011). Several occupational assessments conducted in the region have demonstrated that sugarcane workers perform heavy manual labor in high ambient temperatures, increasing risk of heat stress (Crowe, 2010; Crowe, 2009; Cortez, 2009; Kjellstrom 2011). An occupational assessment conducted by Boston University in the Ingenio San Antonio in April 2010 demonstrated that sugarcane workers perform heavy manual labor in high ambient temperatures and therefore have a high risk of heat stress that likely varies by job task (i.e. cane cutter vs. irrigator) (BU, 2010b).

Although heat stress is not a recognized cause of CKD, it is associated with volume depletion and muscle damage (rhabdomyolysis), both of which are recognized susceptibility factors of *acute* kidney injury (AKI) (Kew, 1970; Demos, 1974; Schrier, 1967). There is an incipient but growing body of literature that speculates whether recovery from AKI (reversible kidney failure) in hospitalized patients, or even acute kidney *damage* (understood as subclinical and reversible damage, e.g. fluctuations in the creatinine level) may leave residual structural damage and eventually progress to CKD later in life (Chawla, 2011; Goldstein, 2008; Levin, 2008; Venkatachalam, 2010; Yang, 2011).

In addition to being associated with CKD, dehydration was considered by physicians and many pharmacists to play a role in the frequent occurrence of "chistata", a compilation of symptoms roughly synonymous with dysuria, in the region. Dysuria is usually considered to be a symptom of an underlying UTI, STI, kidney stones, or, far less commonly, malignancies of the urinary system (i.e., bladder or prostate cancer).

According to both physicians and pharmacists interviewed, urinary tract infections[5] and dehydration are the two main causes of chistata. This finding is of particular interest, as incidence of UTI in the global population generally, and in the US specifically, is higher and relatively common among females compared to males. In the US, diagnosis of UTI in males generally is associated with a urinary tract malformation or obstruction that must be identified by imaging and then treated to suppress the cause of infection and prevent recurrence (Shaeffer, 1994).

Determining whether or not the dysuria-related symptoms in Nicaragua mentioned by pharmacists and physicians correspond to underlying urinary tract infections would require the use of further diagnostic tools. The understanding gained through the interviews is that the most commonly available diagnostic tool at primary health centers is a urine analysis, which includes a urine dipstick and a light microscopy of urine samples. The urine dipstick is the easiest means of diagnosing UTI qualitatively. This test detects white blood cells (leukocytes) and nitrites in urine. Simultaneous detection of the two is highly sensitive[6] and suggestive of UTI, being the most common cost-effective test to presume a UTI (especially among women) and start treatment with antibiotics. Nevertheless, the gold standard diagnosis is to identify the urologic pathogen with a urine culture, which, according to the interviewees, is not widely available in Nicaragua, unless patients are referred to a hospital or pay it out of pocket in a private facility. Also, imaging techniques may be necessary in order to rule out kidney stones and anatomic abnormalities, both causes of obstructive nephropathy and vesico-ureteral reflux, which are also potential causes of CKD. While recurrent UTIs were mentioned by physicians and pharmacists as potential causes of CKD in the area, there was far less agreement about the role of kidney stones in the etiology of CKD, with some certain of the contribution of CKD, and others not supporting this possibility.

The lack of diagnostic tools to identify the pathogen responsible for UTI begs the question of whether the diagnosis of UTI by physicians in this region is truly identifying an infection. We could speculate, on one hand, that the dysuria-related symptoms presented mostly by field workers could be due to crystaluria or precipitation of uric acid due to dehydration. On the other hand, there may be something other than infectious pathogens causing the white blood cells in urine to increase. The finding of significant numbers of white cells in urine without bacterial growth, is known as aseptic leukocyturia, and can develop from various causes. The use

[5] UTI can be restricted to the bladder (essentially in females) referred to as lower tract urinary infections, or it can involve a solid organ (the kidneys- in both genders- named "pyelonephritis", and the prostate in males).

[6] This test is 95% sensitive and 75% specific, and its negative predictive value is close to 96% (Pappas, 1991). Check reference for positive predictive value and population used.

of (antibiotics) before urinalysis is believed to be the most common cause of aseptic leukocyturia, but other causes include kidney stones, and chronic interstitial nephritis (i.e. CKD).

The frequent occurrence of "UTI" was also identified during the abstraction of clinical information of 61 workers randomly selected at the Ingenio San Antonio as part of a pilot cohort study; we found that almost 70% of the workers whose records we reviewed were diagnosed with a UTI on at least one occasion. The diagnosis of UTI was recurrent, with workers receiving a diagnosis of UTI up to 17 times (median=1.5). Dysuria (with or without fever and back pain) was present in around 40% of medical encounters with a diagnosis of UTI (n= 140), back pain (with or without fever) in 21.4% and fever in 5.7%. Only 40% of the medical encounters where a diagnosis of UTI was given had a documented urinalysis (no cultures were performed) accompanying this diagnosis, with half showing evidence of white cells in urine microscopy. Like two of the physicians interviewed, our BU team also concluded that UTI was most likely over-diagnosed among workers. The true cause of pain and UTI-like symptoms, however, warrants further investigation (BU, 2011). We could explore the specific hypothesis that a finding of white cells in urine (in the context described above) could also be due to an ongoing chronic interstitial injury or damage. The question then would be what is causing that chronic kidney damage. Systemic infections involving acute kidney injury, such as leptospirosis (named by one physician as a prevalent disease in the region) or hantavirus, could be hypothesized, as well as the role of heat stress, exposure to agrichemicals, or known nephrotoxicants such as heavy metals, some antibiotics and NSAIDs,

Interviews also provided evidence suggesting that diuretics, antibiotics and NSAIDs are widely used and sold over the counter for very general symptoms. Drugs mentioned included antibiotics such as quinolones (Ciprofloxacin, Norfloxacin, Levofloxacin and Nalidixic acid), penicillins and cephalosporins (Amoxiciline, Cefadroxil, Ceftriaxone) and Trimethoprim-sulfamethoxazole, all of which could cause allergic interstitial nephritis (AIN) as an adverse effect. Sulpha-related diuretics could also show this adverse effect. Phenazopiridine (Pyridium®), a widely used drug in the region according to physicians and pharmacists, may cause acute kidney injury (AKI) but only in the setting of causing methemoglobinemia and hemolytic anemia. Both described events are rather rare, and non-dose dependent and most probably do not have any relevance in the Nicaraguan context. On the other hand, aminoglycoside antibiotics (such as Amikacin and Gentamicine) are known to cause both AKI in a dose and duration dependent manner, and progression to CKD. This type of antibiotic was named by both pharmacists and physicians (who more frequently cautioned about its nephrotoxicity) as being used in the region. Lastly, chronic use of NSAIDs such as Ibuprofen, Naproxen and Diclofenac is also known to cause AKI and CKD in correlation with the dose and frequency of use. The nephrotoxicity of both aminoglycosides and NSAIDs could be aggravated by dehydration. The use of diuretics as indicated by some interviewees could contribute to volume depletion states where the use of these nephrotoxic drugs could result in kidney injury.

Remarkably, pharmacists did not distinguish between chistata, UTIs and CKD, considering all of them different forms or degrees of the same kidney disease, usually treated with antibiotics with or without a formal diagnosis by a physician. Reasons for this fact appeared to be lack of adequate access to health care (barriers named included aspects related to lack of

diagnostic tests and treatment at various health care facilities, health illiteracy and poverty), and a tremendous pressure placed by customers on pharmacists to give medications over the counter This makes it plausible that patients with already some degree of CKD are more likely to be receiving nephrotoxic drugs. Furthermore, the lack of resources to make an early diagnosis of CKD in the area, as pointed out by several physicians, may make a substantial part of the population unaware of their already deteriorated kidney function.

A summary of drugs' nephrotoxicities and medical conditions associated with kidney damage are presented in the table below.

Table 2: Types of kidney damage by drugs and medical conditions.

Type of drug	**Drug**	**Type of kidney damage**	**Setting**	**Findings**
Urinary analgesic/antiseptic	Phenazopiridine (Pyridium)	Acute Kidney Injury (AKI)	Only in the setting of causing methemoglobinemia and hemolytic anemia	
Trimethoprim-sulfamethoxazole (antibiotic)	Sulfamethoxazole	Allergic Interstitial Nephritis (AIN)	Rare Non dose dependent	eosinophilia and rash occur in less than 40%
Quinolones antibiotics	Ciprofloxacin Norfloxacin Levofloxacin Nalidixic acid	Allergic Interstitial Nephritis (AIN)	Rare Non dose dependent	eosinophilia and rash occur ins less than 40%
Penicillins and cephalosporins (antibiotics)	Amoxiciline Cefadroxil Ceftriaxone	Allergic Interstitial Nephritis (AIN)	Rare Non dose dependent	eosinophilia and rash occur in less than 40%
Aminoglycoside (antibiotics)	Amikazin Gentamicine	ATN, Acute tubular necrosis (a type of AKI) -If progression to decreased Glomerular Filtration Rate, causes **CKD**	Dose and duration dependent Important context of dehydration	-muddy brown granular, renal tubular epithelial cells casts(neither of which are detected by dipstick) and white cells. -Depending on the degree of inflammation, leukocyte esterase may be + as well as low grade albuminuria. -may not see a substantial rise in the serum creatinine
Sulpha-related diuretics	Furosemide Thiazides	Allergic Interstitial Nephritis (AIN)	Rare Non dose dependent Contribute to volume depletion	
NSAID	Ibuprofen Naproxen Diclofenac	Acute Interstitial Nephritis (AIN) and acute tubular necrosis (types of AKI) and chronic interstitial nephritis -If progression to decreased Glomerular Filtration Rate, causes **CKD**	Dose and duration dependent Important context of dehydration	often but not always associated with nephrotic syndrome, usually minimal change disease but occasionally membranous nephropathy
Other analgesics: APC	APC: a combination of aspirin, phenacetin and caffeine **(Excedrin)**	There is not enough scientific evidence (few references) regarding an association with CKD		
UTIs	Not proven with low urinary tract infections	Inflammatory reactions that contribute to renal	Very difficult to diagnose	Usually in the context of anatomic abnormality like vesico-ureteral reflux and /or

	Maybe with chronic or repeated pyelonephritis	lesions and scarring that hypothetically could end in **CKD**		an obstruction
Nephrolithiasis		Both through an obstructive uropathy and uric acid pathology.		

Source: Adapted from Schrier, 1999.

The pharmacists had contradictory impressions of how drinking water plays a role in CKD, with half the pharmacists believing that dehydration (i.e., not drinking enough water) leads to CKD, and the other half believing that CKD may be caused by contaminated drinking water. These beliefs would result in quite different opinions of action to prevent CKD, both of which could have the opposite effect. These perceptions by pharmacists and their ramifications deserve further attention.

While some physicians acknowledged an improvement in diagnostic tools, lab facilities for screening and diagnosis, and treatment of CKD in the area over the past years, they also perceived that these may not be enough to address the CKD epidemic, resulting in delayed diagnosis of CKD, limited ability to rule out other related diseases (kidney stones, UTIs, etc), and scarce access to CKD referral and treatment, especially for ESRD (i.e. dialysis). Similar findings resulted from in-depth medical needs and gaps in quality of care assessment conducted recently in the area (CAO, 2011). Issues such as CKD early diagnosis, case-definition, referrals and treatment are addressed in the "National Normative and Protocol of CKD" of the Nicaraguan Ministry of Health, with contributions by several nephrologists and clinicians of the country, dated 2009 (MINSA, 2009). Nevertheless, only two physicians knew the existence or implementation of such guidelines, with one other physician even requesting more training on this health issue.

In summary, these interviews have highlighted several potential contributors to CKD in Nicaragua and medical conditions that may be related to CKD. They have also helped us to identify beliefs and practices (about use of diuretics, bathing and drinking water) that could contribute to kidney damage. Limitations of our study include the small number of physicians and pharmacists interviewed, and the inability to determine whether or not everyone interviewed was telling the truth (e.g., about the dispensing of medications) or saying what they thought was the best or most acceptable answer. This is a limitation of all interview and survey methods. Despite these limitations, information from these interviews is valuable and suggest several areas for further investigation in Nicaragua, for example on potential association between UTI diagnosis and/or medication use and subsequent development of CKD, and the possibility of kidney damage early in life leading to CKD later in life.

RECOMMENDATIONS

Physicians and pharmacists interviewed in this study reminded researchers that the CKD epidemic is an extremely challenging health problem for communities, the health care system and the private sector, with deep social and economic impact, that grants further public health intervention aimed to reduce the burden of the disease in the region. Following is a summary of our recommendations, based on our findings, organized around the areas of 1) primary prevention, 2) secondary prevention, 3) further research, and 4) training.

1) **Primary prevention: Efforts to prevent the occurrence of CKD.**

- **Experience of heat stress as a cause of CKD** was the primary hypothesis to emerge from the interviews. Heat stress is likely to involve exposure to hot sun, physical work and dehydration. The role of heat stress in the development of CKD is still not clear, but its plausibility together with a high likelihood of exposure in Nicaragua lead to the recommendation for a **population-based health promotion intervention**. Some large employers of the area (i.e. sugar cane companies) have already established rehydration programs among their workers. These and similar programs should attempt to address community and workers´ concerns about water safety, as the sources of water at work and within the community may be perceived as contaminated by agrichemicals or heavy metals, which are believed to cause CKD. Employers should also be aware of the possibility that there may be cultural beliefs regarding drinking water while hot (and sudden change of temperature) and educate workers on the importance of hydrating. Further steps to reduce the risk of heat stress (as proposed by BU, 2011b) should also be considered (e.g. acclimatization programs, supervised breaks, etc).

- The interviews provided insight about the wide use among the community and workers of nephrotoxic medications such as NSAIDs or aminoglycoside antibiotics and/or of diuretics, that may enhance volume depletion states. Furthermore, the patients with "UTI" or chistata may actually have some degree of undiagnosed kidney damage and are more likely to be receiving nephrotoxic drugs. **Patient's safety control programs** addressing the adverse effects and the prescriptions or selling over the counter of the mentioned drugs should be put in place and may require an effort to share information and provide training with pharmacists and physicians throughout the region.

2) **Secondary prevention: Efforts aimed at early disease detection, thereby increasing opportunities for interventions to prevent progression of the disease and emergence of symptoms.**

- Early recognition and intervention are essential to slow disease progression, maintaining quality of life and improving outcomes. Implementation of the **National CKD Norm and Protocol** and provision of a comprehensive response to CKD in the area (including aspects mentioned by physicians such as nutrition, psychological support, training of health care resources, etc) seem to be critical to the secondary prevention of CKD. A coordinated effort of public and private institutions (at local, national and international levels) should be consolidated in order to guarantee access to early detection of the

disease, required differential diagnosis with other medical conditions (UTI, kidney stones), and continuous health care of CKD patients.

3) **Further research**: There is an urgent need for research on the true incidence and prevalence of all stages of CKD, its risk factors and other medical related conditions, in different populations in Nicaragua.

- **Information systems of epidemiological surveillance** integrated both at work places and in the health system should be put in place and/or reinforced.

- **Research of heat stress, causes of dysuria and white cells** (UTI, systemic infections such as leptospirosis, renal calculi, etc), is of high priority. Research involving a detailed exposure assessment (estimation of concentration, events of exposures and biomarker doses in blood and urine) and a dose-response assessment are key to further characterize and estimate risk among different populations.

4) **Training of health resources and pharmacists** plus **community education programs**, seem to be key to implement all these recommendations and tackle the disease in a meaningful and sustainable way in the region.

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APPENDIX I: INTERVIEW GUIDES

Physician Interview Guide

My name is [name interviewer]. I am working with a research team from Boston University School of Public Health studying kidney disease in Nicaragua.

Introductory:

1. **Please state in your own words who you are, and where you are working.**

2. **How long have you been practicing in Nicaragua?**

3. **How would you describe the population that you treat or provide care for?**

   [Probe: age, sex, occupation.]

Chronic Kidney Disease:

4. **What can you tell me about Chronic Renal Insufficiency (CRI)? Do you think it is a problem in Nicaragua?**

5. **Has the number of cases you see each year changed in the time you have been in practice?**

6. **How would you describe the affected population?**

   [Probe: men compared with women? young v. old? geographically concentrated? some occupations more than others?]

7. **What are symptoms of CRI that you have observed?**

8. **What medications do you prescribe to treat CRI?**

   What resources, if any, do you rely on for standards of diagnosis and treatment?

   [Probe: do they rely on MINSA or other standards? Nothing? Their own experience/familiarity with CRI?]

9. **What tests, if any, do you rely on for making diagnoses? In other words, what defines CRI?**

   [Probe: Is there a particular creatinine level?]

10. **How long, in your opinion, do people with CRI live past diagnosis?**

11. Do the patients you see with CRI have much protein in the urine?

12. What do you think are causes of CRI in Nicaragua?

[Allow them to elaborate on systemic causes of CRI, immune, etc.]

[Probe: Ask about diabetes and high blood pressure]

13. Do you often treat the spouses, children or families of your patients?
   a. Do you think CRI may run in families?

14. In the US there are differences in CRI by race or ethnicity. For example, blacks or afrodecendents have more probability to develop CRI and disease progresses faster. Do you observe any differences in Nicaragua between people with different ethnic groups or culture?

Chistata:

15. I'd like to ask you questions now about a condition I've heard described as "Chistata." Can you tell me, what is "Chistata"?

16. Do you use the term, Chistata, or is there another term that you use to describe this condition?

[Probe: urethritis?]

17. What are the symptoms of Chistata?

18. What do you think is the cause?

[Probe: STDs, dehydration, renal calculi, local trauma in lower UT]

19. How do you treat Chistata?

Other Conditions:

20. Do you see many Sexually Transmitted infections (STIs) in your practice?

21. **What diagnostic tests do you take?**

[Probe: blood tests, cultures, pap smear?]

22. What tests do you do, regularly, if any, on a patient complaining of lower back pain?

23. What determines the tests you are likely to have?

[Probe: lab costs, beliefs about blood taking? Why or why not re. urine cultures? How often, why / why not?]

24. **Do you diagnose UTIs? How often? On what basis / evidence?**

25. **How often do you treat without doing a urine culture?**

26. **How do you treat UTIs?**

27. **In your opinion, are STIs, UTIs and Chistata potential precursors of CRI, or in any way related?**

28. **Have you seen a lot of patients with kidney stones/calculi?**

29. **What other health outcomes do you see often in your practice that may be related to CRI?**

    [Probe: hearing loss? Hypertension, diabetes, heart disease,]

30. **How about outcomes that may not be related to CRI?**

    [Probe: reproductive, nervous system, respiratory, arthritis, immune diseases]

General:

-

31. **We have heard from people who work in sugarcane that changes in temperature (from hot to cold) may be dangerous. For example, drinking cold water when hot, or having a shower after a long day of hot work? In your opinion, are any negative health outcomes likely to result from this type of behavior?**

32. **Do you ever ask patients about whether or not they take herbal remedies or see traditional healers?**

    [Probe: what types of healers? What types of medications? What is their opinion of these natural medicines?]

Medications:

We are getting close to the end of the interview. I'd like now to ask you about specific medications.

33. **Please tell me, for each of the following, if you prescribe these medications, for what reasons. And if no, why not?**
    a. Pyridium (fenazopiridina)

    b. Nalidixic acid.

c. nitrofurantoína

d. furazolidona

e. NSAIDs

f. Other antibiotics

g. Gentamicin

34. Finally, where else have you practiced and for long have you been practicing?

Thank you very much. I am finished with my questions. Is there anything else you would like to tell me?

Pharmacist Interview Guide

My name is [name of interviewer]. I am working with a research team from Boston University School of Public Health studying kidney disease in Nicaragua.

Introductory:

14. Please state in your own words who you are, and where you are working.

15. How long have you been practicing in Nicaragua?

16. How would you describe the population that you see in your pharmacy?

[Probe: age, sex, occupation.]

Chronic Kidney Disease:

17. What can you tell me about Chronic Renal Insufficiency (CRI)? Do you think it is a problem in Nicaragua?

18. Has the number of cases you see each year changed in the time you have been in practice?

19. How would you describe the affected population?

[Probe: men compared with women? young v. old? geographically concentrated? some occupations more than others?]

20. What prescriptions do you fill to treat CRI?

21. Does everyone who comes for medications have prescriptions from their doctor, or do you also tell people what medications they need?

22. What are symptoms of CRI?

23. What do you think are causes of CRI in Nicaragua?

24. Do you think CRI may run in families?

25. In the US there are differences in CRI by race or ethnicity. For example, blacks or afrodecendents have more probability to develop CRI and disease progresses faster. Do you observe any differences in Nicaragua between people with different ethnic groups or culture?

Chistata:

26. I'd like to ask you questions now about a condition I've heard described as "Chistata." Can you tell me, what is "Chistata"?

27. Do you use the term, Chistata, or is there another term that you use to describe this condition?

[Probe: urethritis?]

22. What are the symptoms of Chistata?

23. What do you think is the cause?

[Probe: STDs, dehydration, renal calculi, local trauma in lower UT]

24. With what medication is Chistata treated?

Other Conditions:

25. Do you fill prescriptions for many Sexually Transmitted infections (STIs)?

26. **How do you treat UTIs?**

27. **If a patient complained of lower back pain, how would you advise them?**

28. **In your opinion, are STIs, UTIs and Chistata potential precursors of CRI, or in any way related?**

29. **Have you seen a lot of patients with kidney stones/calculi?**

General:

-

30. **Do you ever ask patients about whether or not they take herbal remedies or see traditional healers?**

    [Probe: what types of healers? What types of medications? What is their opinion of these natural medicines?]

Medications:

We are getting close to the end of the interview. I'd like now to ask you about specific medications.

31. **Please tell me, for each of the following, if you fill prescriptions for these medications, for what reasons. And if no, why not?**
    a. Pyridium (fenazopiridina)
    b. Nalidixic acid.
    c. nitrofurantoína
    d. furazolidona
    e. NSAIDs (get brand names… don't ask about "NSAIDs")
    f. Other antibiotics
    g. Gentamicin

Thank you very much. I am finished with my questions. Is there anything else you would like to tell me?

APPENDIX II: SUMMARY OF FINDINGS NOT INCLUDED IN REPORT.

When physicians were asked about **Sexually Transmitted Infections or STIs**, we got an ample range of responses regarding their frequency. Internal medicine and nephrology specialists admitted they don't get to see them because they are diagnosed and treated at the primary health care level (special STI programs) or at most by gynecologists and urologists, and they are not familiar with those statistics. One internal medicine doctor said they were very common, two primary health care doctors specified they are very common, and one other said that its occurrence it's very little.

STIs named include trichomoniasis, vaginal yeasts (candidiasis), genital warts or "Condyloma acuminate", Granuloma inguinale, chlamydias, syphilis, gonorrhea, and HIV. Common diagnostic tools were: physical exploration, urine analysis, vaginal exudate or urethral discharge gram stains and cultures, VDRL and RPR syphilis tests, and HIV test.

When pharmacists were asked about STIs and whether they fill many prescriptions for them, 5 pharmacists said "no or very little". Symptoms or infections named by four pharmacists include itching, discharge, gonorrhea, and "rooster crests" (genital warts or "Condyloma acuminate"). Available treatments are penicillin- probenecid, metronidazole-nystatin, sulfonamides, clindamycin, dexamethasone. Three pharmacists stated how challenging the provision of care or treatment of this sort is:

> "Well, I try and convince them to go and get a pap smear. But there are people who don't go…. Like I said, people come almost looking for a doctor…. And I say, Do you want me to perform miracles?" (Pharmacist B).
>
> "Mostly women are coming and you give them the treatment, but if the couple doesn't want it, it doesn't work. And men are very machista" (Pharmacist A).
>
> "They come saying they sat on a contaminated toilet and that they began itching, things like that. So I give out medication. Sometimes they come asking clearly for it, especially penicillin" (Pharmacist I).

None of the physicians, and most pharmacists (8 out of 9), thought STIs could have any role in the CKD epidemic in the area. One physician established the connection between chistata and STIs but thought that only renal infections could play a role in the CKD epidemic. One pharmacist said that untreated STIs (as well as UTIs) could lead to CKD.

Healers and herbal remedies

Physicians and Pharmacists had similarly varied responses to the question of whether or not patients take herbal remedies or see traditional healers. They ranged from "No, here this is not a habit and there are no traditional healers" (Pharm F) to "I myself take a lot of herbal remedies… for infection, for my kidneys. I also take an aloe drink. I recommend people to take it because it works for me" (Pharm H). Two physicians also mentioned aloe vera as an herbal remedy patients sometimes take (Phys 1, 4).

Five of nine pharmacists had vague responses to the question, indicating little knowledge of, and little interest in, herbal remedies or traditional healing practices (Pharm A, B, C, D, G). Two pharmacists (E, I) said that yes, patients take herbal remedies, with Pharm E saying "there are many people who go to a healer." Both named the herbal remedies they knew of, including something called horse tail (cola de caballo). One physician also mentioned horsetail (Phys 1)

Physicians had more ideas about herbal remedies taken by patients, with all 10 physicians indicating that in fact their patients are likely to take herbs, and three implying that they might not take them so much anymore. As for seeing traditional healers, responses were mixed, with Phys 2 and 10 saying without a doubt people go to traditional healers or witch doctors (curanderos) and Phys 6 saying "regarding healers, a little. Before I remember they used them a lot, but now I don't see much." Phys 8 speculated that patients "come up with a story" about their neighbor or a friend who told them something, "But the patient does not come and say, 'I went to the herbalist' directly."

In terms of what herbal remedies patients might be taking four physicians referenced the noni plant, also referred to as morinda:

> "There is a fruit called noni. Noni is used for everything. People believe it is a miracle fruit. I can't recall others, but the truth is that I am not very interested in this. But noni does spark my attention because there are people that abandon treatment to start taking noni." (Phys 2)

According to Phys 5, noni was used a lot in the last four years by renal patients, and "it led various patients to intensive car, poisoned with progressing CRI, that had to go into dialysis." Phys 3, however, referred to a boom of noni taking, but said "not anymore."

The combined list of remedies from physicians and pharmacists included chamomile (Phys 4, 5, 6, 8); cats tail (una de gato) (Phys 2); cats claw (Phys 4); ceiba leaf (Phys 1); tree barks (guarumo) (Phys 1); bitter orange (Phys 4); oregano (Phys 5, 6, 8); eucalyptus (Phys 5, 6); Sardinillo, Sasparilla and calabash (Phys 7); llanten from a small bush (Pharm I), and sugarcane, "You mash up the sugarcane and leave it in water, that you drink the water all through the day. Always for kidney problems." (Pharm I.)

Physician 1 mentioned a concern about plants that have alkaloids that may damage the kidney.

CKD treatment by physicians

Regarding medications prescribed to CKD patients, all physicians agreed that treatment somehow targets only symptoms, co-morbidities and sequelae such as hypertension or anemia, but CKD is irreversible.

We do not have the medications that we would like to have, but I think we do well, more or less with what we have" (Physician 2).

ACE inhibitors such as enalapril or captopril are the preferred medications for hypertension treatment, specified by 9 of the physicians. ARA II (angiotensin II receptor antagonists) were mentioned by two physicians (Phy 1 and 4), with one of them remarking that

these are not usually covered by the MoH's list of essential medicines for any conditions (which means that patients can only get them if they can afford to pay for them, as the MOH does not subsidize their use. (Phy 4). Only one physician would say that they may use sometimes atenolol or any other Beta blocker drug (Phy 10), and in two other occasions amlodipine or, more broadly, a calcium channel blocker (Phy 2, 4), if for any reason the first line treatment cannot be used (Phy 4). Four physicians said they would have to use diuretics at certain times (e.g. to treat edemas), but that they were not routinely used (Phy 2, 4, 7, 9).

All physicians addressed treatment for anemia. Nine of them would prescribe iron or ferreous sulphate supplements. Three doctors said that erythropoietin was only available at the hospital level or at patients' out of pocket discretion. Doctors from hospitals would confirm that erythropoietin is available for patients enrolled in dialysis programs (provided by the MoH), though one said that they got it for the first time recently.

Allopurinol, as a drug to bring down levels of uric acid, was mentioned by five of the ten physicians (Phy 2, 3, 4, 5, 9). Nine of them mentioned that they would prescribe calcium supplements and, one, vitamin D (Phy 6) for hypocalcemia. One mentioned statin therapy with atorvastatin or simvastatin for patients with dyslipidemia (Phy 2).

Four physicians mentioned nutrition (eg. dietary protein or salt restriction) as being a critical aspect for self-care and health promotion of renal patients (Phy 3,5,6,8). Two of them mentioned nutrition when referring to the improvement of the prognosis of renal patients (Phy 1, 10).

"Also, healthy lifestyle changes, hypoproteic, hyposodic diet, limiting themselves to long exposures to the sun, adequate water intake, consumption according to doctor's orders and the relative amount of rest, according to recommendations. At the same time family support for these patients' nutrition. It has to be a little lower in fats and adequate enough so as to not keep up the renal protein overload" (Physician 5).