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EDITORIAL

Chronic Kidney Disease in the Developing World: An Iceberg Turned Volcano

Internationally, chronic kidney disease (CKD) has been compared to an iceberg: one million people worldwide with end-stage renal failure form the visible tip, while tens of millions more with some degree of kidney dysfunction lurk below. Nevertheless, 90% of those already diagnosed and receiving renal replacement therapy (RRT) are from the developed world. This, leads one to wonder if the underwater mass estimates are not themselves a product of the sorely under-reported, early CKD in the global South - where the looming threat might better be characterized as volcanic. Its eruption threatening to crush precarious health systems already struggling under the double burden of infectious and emerging chronic diseases.[1]

In the West, about 60% of all patients with end-stage renal failure have diabetes and hypertension, the two conditions paving the road to CKD. The global epidemic of type-2 diabetes is expected to reach 400 million people by 2030. The more disturbing underlying reality is that while prevalence in developed nations is projected to increase by 60-70%, the increase in developing countries is expecting a 250% explosion.[2] U.S. spending on its ESRD program reached a record $25.2 billion in 2002 (an 11.2% increase over 2001),[3] making it clear that Third World countries and their health systems have no way to financially confront this crisis, and will be forced to leave millions to die without treatment. Thus, CKD and related chronic conditions will become the “silent partners” of HIV/AIDS and other infectious killers.

At its ground-breaking meeting in March, 2004 - “Preventing the Progression of Kidney Disease: Toward Global Equity” - the International Society of Nephrology convened experts in the field at the Bellagio Study Center to address these chilling facts, which threaten to exacerbate health disparities and the “health care divide” worldwide. They called upon the international medical community, governments, and financing agencies to work together in an all-out effort to stem the tide of the epidemic, and to develop evidence-based prevention strategies workable for resource-poor health systems, giving priority to “the regions of the world showing greatest risk.”[4]

Without a doubt, one of those regions is Central America and the Caribbean, where the epidemiological picture contains two additional elements predisposing its populations to CKD risk. First, its ethnic-racial composition is similar in many ways to U.S. minority communities, with significant indigenous and African Diaspora segments, which in the USA exhibit ESRD incidence rates at twice and nearly four times the rates as whites, respectively.[3] Second is the presence of widespread poverty itself (40%): low socioeconomic status has been identified as a risk factor for development of renal insufficiency in research such as the Multiple Risk Factors Intervention Study (MRFIT).[1] Yet, recent data from the Latin American Registry (2001) indicates that, except for Puerto Rico, the incidence of chronic patients in dialysis in Central America and the Caribbean is 60 pmp or less, and prevalence in dialysis is less than 100 pmp. This suggests that the region already faces a crisis of under-diagnosis and under-reporting of substantial consequence.

Such a pressing situation has prompted the 9th Central American and Caribbean Congress on Nephrology and Hypertension, held this month in Cuba, to adopt prevention of CKD as its main theme (see Specialists Look at Renal Disease in the Region). Participants will be drawing on accumulated findings and dialogue to more clearly define options for formulating preventive strategies.

In this month’s MEDICC Review, we share with you aspects of the Cuban experience in prevention and comprehensive management of CKD, as the Cuban “school of nephrology” advances within the international current of prevention-based approaches (MR Interview: Round Table with Two Generations of Cuban Nephrologists). A guest Spotlight column by Dr. Raúl Herrera outlines Cuba’s National Program for Chronic Kidney Disease, Dialysis and Renal Transplantation.

In Effect of Primary Health Care in Cuba on the Prevention of Chronic Kidney Disease, Dr. Miguel Almaguer examines the impact of the neighborhood doctor program on preventive practices islandwide, especially the role of family physicians, who now provide nearly 100% national coverage.

We are especially pleased to reflect two very recent developments in Cuban nephrology as they relate to health outcomes: the first concerns the expansion of dialysis centers in the country from 31 to 47, on the basis of a national study of chronic renal patients (Bringing Services Closer to Home: MR Visits a New Dialysis Center in Cuba). The second is a set of new research, involving three separate studies whose goal is national implementation of effective prevention strategies for CKD and related chronic conditions (Cuban Studies Aim for National CKD Prevention). Initial results of a pioneering study in total population on Cuba’s Isle of Youth are being presented at the Central American and Caribbean Congress, and will be reported in our June issue.

Among the longer-term objectives of the Cuban research is to study the increasingly evident and complex relationship among illnesses sharing vascular damage as a common denominator - CKD, cardiovascular disease, diabetes, hypertension, and cerebrovascular disease among them. The obvious importance of this and similar investigations is their potential to lead to adoption of comprehensive prevention programs, beginning at the community level, for this entire group of chronic conditions. In this context, early diagnosis of vascular damage among children takes on added significance (Hypertension in Children: Diagnosis and Treatment for Renovascular Hypertension over a 15-Year Period).
Several articles in this issue reflect experience in the development and use of Cuban products: the first two in renal patients (Broad Use of Cuban Recombinant Human Erythropoietin (EPOCIM) Hemodialysis Patients at the Institute of Nephrology and Use of Recombinant Streptokinase for Hemodialysis Catheter Recovery), and the third describing a breakthrough in late April, as Cuban scientists announced the successful completion of clinical trials on a new cholera vaccine (Cuba Announces New Cholera Vaccine at “Health for All” Trade Fair).

You’ll find our news this month reflects key developments mainly in international cooperation, from our Top Story: Cuba Marks 15 Years of Treating Chernobyl Victims, to headlines including A Decade of Medical Donations Cements Cuba-Canada Cooperation, and Running for a Cure: Terry Fox Inspires Cuba.

Last but certainly not least, we carry the story of 34-year-old Hector Despaigne of eastern Cuba, Latin America’s Longest Heart Transplant Survivor, 19 Years Later - a living reminder that developing nations’ potential is not only in broad-based prevention, but also can, and should be, in generating the human resources and institutions capable of integrating and making accessible the latest techniques of modern science.

The Editors

SPOTLIGHT

Cuba’s National Program for Chronic Kidney Disease, Dialysis and Renal Transplantation

By Raúl Herrera Valdés, MD, PhD

In the Central American and Caribbean context, Cuba shares many of the economic limitations suffered by other countries. At the same time, Cuba has advanced along the route of equity described by PAHO as critical to improving health in the region, being one of the least socially stratified countries in the area. [1] In addition, 96.2% of the country’s adult population is literate and the average educational level is ninth grade. The health system is universal, public, and free-of-charge, with coverage extended to 100% of the population.

Cuba’s resource-scarce environment, coupled with public health principles, has reinforced a commitment to primary health care and prevention as the centerpiece of the system. Cuba’s infant mortality is 5.8 per 1,000 live births (2004); and the main causes of death are non-communicable chronic diseases, with only 1% from communicable diseases. The Cuban population is one of the fastest aging in the Americas.

Significant attention has been paid to developing human resources in health, resulting in 60.4 physicians per 10,000 inhabitants [2].

National Chronic Renal Disease Program

In today’s world, the epidemic evolution of chronic renal insufficiency constitutes a serious problem, the implications of which are not only medical, but also social, economic, organizational and political. The fact that end-stage renal disease (ESRD) is a phased process suggests that prevention should be applied in all phases, beginning with healthy individuals and risk groups. As a result, in 1996 a national program was approved, offering essential guidelines for prevention, based on continuing evaluation of the epidemiological situation and progressive incorporation of preventive strategies at all levels of care.

Epidemiological Background of CKD in Cuba

In 1988, a study was carried out in Pinar del Río Province (population: 700,000), on a sample of complete families - 11,804 persons in all - under the regular care of 21 family physicians in ten municipalities. Of these, 9,580 persons were screened, or 81% of the total sample. Screening revealed 34 persons with serum creatinine levels above 1.2 mg/dl. Only two of these, or 6%, had

References


3) US Renal Data System. USRDS 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2004. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

The National Program

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National CKD, Dialysis and Renal Transplantation Program (linked to primary care physicians and hospitals across the country), oversees organ procurement and the national organ bank; trains specialists in nephrology; and carries out about 40 kidney transplants annually. Currently, some 120 patients also receive dialysis at the Institute.

The Institute’s design - integrating prevention (through the national program and training of family doctors), clinical nephrology, dialysis, transplantation and research - is unique in the field of nephrology, with perhaps only one other institution of its kind in the world.

Brief History and Description: The Institute of Nephrology was founded in 1966 under the leadership of one of Latin America’s outstanding specialists in the field, Dr. Abelardo Buch López, whose name the Institute bears today. The facility is one of eight clinical institutes in Cuba’s health system.

The Institute’s staff includes over 100 professionals, including specialists in 13 fields. Of these, 30 carry out teaching functions in the education of residents in nephrology.

The Institute’s five-story, 91-bed structure houses units responsible for: Hemodialysis, Renal Transplantation, Intensive Care, Clinical Nephrology, Surgery and Laboratories (Renal Physiopathology, Transplant Immunology, Clinical Biochemistry, Nuclear Medicine, Preventive Epidemiology and Pathology, among others).

In an effort that is just beginning, a total of 280 nephrologists and 150 residents have been distributed regionally in 47 hospital-based nephrology services. From these centers, they will provide essential guidance in prevention and treatment of renal disease for the country’s family physicians across the country, through the 444 community polyclinics where the family doctors are clustered. Completing the infrastructure are 33 hospitals for organ procurement, nine renal transplantation centers, and five tissue-typing laboratories[2,5].

Implementation of Prevention Strategies: Resources and Infrastructure

In an effort that is just beginning, a total of 280 nephrologists and 150 residents have been distributed regionally in 47 hospital-based nephrology services. From these centers, they will provide essential guidance in prevention and treatment of renal disease for the country’s family physicians across the country, through the 444 community polyclinics where the family doctors are clustered. Completing the infrastructure are 33 hospitals for organ procurement, nine renal transplantation centers, and five tissue-typing laboratories[2,5].

National Direction and Coordination

The Program is directed and coordinated by the Institute of Nephrology, the national reference center for the specialty, which is also responsible for developing human resources in the field, generating scientific research, and continuously improving levels of patient care.

Perspectives for 2005-2006

The accelerated development of Cuba’s National Nephrology Network over the last two years, strengthened by technological and structural improvements in the Institute itself as national coordinating center, place Cuban nephrology at a qualitatively new stage in its ability to address the comprehensive
management and prevention of renal disease-particularly in its capability to influence health outcomes.

From 2005 forward, the following objectives for Cuban nephrology have been defined:

**General goal:**
Develop an integrative process that includes the transfer and production of scientific knowledge and advanced technology for better understanding and treatment of renal diseases, while facilitating development of a community-oriented preventive strategy to halt the pandemia of chronic kidney disease in its inter-relation with cardiovascular disease, diabetes mellitus and hypertension.

This goal rests on the fulfillment of specific objectives:

1) Consolidate and develop the National Network of Nephrology Services.

   **Facilities:** Over the last two years in Cuba, the number of nephrology services with dialysis increased from 31 to 47. Of the 31 already in existence, new dialysis centers were built in 10; for 2005, new centers will be built in four more and the remaining 17 will be remodeled. In addition, this year one more new service will be opened, bringing the total to 48.

   **Technology:** From 2002 to 2004, the number of artificial kidneys available to patients increased from 303 to 427, or 41%. All dialysis centers are equipped with reverse osmosis water treatment.

   **Human resources:** Over the last two years, 150 new residents have begun their training in nephrology, which will bring to over 400 the number of specialists in the country. This is the highest ratio of nephrologists per inhabitant in Latin America.

   **Indicators:** As a result of the Network’s development, 14.7% more new patients were admitted into dialysis in 2004 compared with 2003, reaching an incidence (new cases per year) of 111 per million inhabitants (pmp). The resulting 11.2% increase in total number of patients in dialysis boosted prevalence to 149 pmp. Internationally, the average increase in prevalence is 7-10% annually. Mortality rates for patients in dialysis also decreased by 8.3%. In 2005, the goal is to continue improving these indicators.[5]

   **Clinical Practice Guidelines in Nephrology:** This year, Cuban guidelines will be written, covering prevention, clinical practice, dialysis and transplantation.

2) Remodel and refurbish the national Institute of Nephrology.

   **Facilities and Technology:** In 2005, the Institute is one of many hospitals being remodeled, increasing the number of beds, creating outpatient services and imaging departments, and improving conditions in the hemodialysis center and laboratories.

   **Human Resources and Teaching:** Forty residents are in training at the Institute. A computer and language laboratory were opened in early 2005, with 18 work stations. The Institute carries out continuing education programs including bibliographic updates, seminars, and specialized courses for professionals and technicians in the various fields represented at the institution.

3) Establish community-based epidemiological laboratories to study the behavior of chronic kidney disease (CKD). In 2005, particular attention is being paid to establishing community-based epidemiological laboratories to study the behavior of CKD, and its relation to cardiovascular disease, diabetes mellitus and hypertension. This is the point of departure for developing a strategy for preventive actions: global actions for the entire population; particular actions for risk groups and for each stage of CKD, addressing the disease’s etiology; and specific actions tailored to each patient. At the same time, medical care should be guaranteed for 100% of newly diagnosed patients. (See MR Feature: Cuban Studies Aim for National CKD Prevention, this issue).

   **Isle of Youth Study (ISYS):** The first of these studies has been initiated on the Isle of Youth, in total population of over 80,000.

   **Havana-Cerro Municipality:** A phased study is being carried out, beginning with a sample of risk groups, including field tests of new models of prevention and care.
**Pinar del Río Province:** A study of 45,000 persons-at-risk is being designed, to analyze and corroborate the studies mentioned above, assessing their application and extension to larger populations.

Parallel to this research, efforts are being made to extend the prevention program, with its already identified actions for controlling risk factors, throughout the whole country. Building upon this and the results of the studies themselves, an important objective will be to offer post-graduate training to family doctors focusing specifically on improving their competency to address non-communicable chronic diseases that have vascular damage as their common denominator. The hypothesis can already be put forward that further training for family doctors may be one way to provide better preventive care and follow-up to 100% of the patients diagnosed through such mass screenings - providing a possible solution to this ethical, as well as clinical, problem.

4) Develop the National Nephrology Informatics Network. In 2005, the National Nephrology Informatics Network is being put in place, made up of three components:

- Linkup for nephrology services among themselves and with the Institute, as their national coordinating center.
- Development of IT infrastructure in the Isle of Youth health system, including the family doctor-nurse offices, and their connection with the national coordinating center.
- Development of the Institute’s intranet capabilities, automating all the Institute’s functions (management, administration, scientific and national coordination activities).

**References and Notes**


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**MR FEATURES**

**Cuban Studies Aim for National CKD Prevention**

By Gail A. Reed

Extrapolating from racial, ethnic and social data of kidney patients in the USA, there is no doubt that the Caribbean and Central America are sitting on a CKD volcano, as our Editorial suggests. The acute problems of cost to health systems and to patients, and of patient accessibility to the latest pharmaceuticals and to renal replacement therapy itself, loom still larger in these resource-poor settings.

At the groundbreaking March 2004 meeting of the ISN’s Commission for the Global Advancement of Nephrology (COMGAN) at the Bellagio Study Center in Italy – “Preventing the Progression of Kidney Disease: Toward Global Equity” - generating knowledge for prevention in developing countries was identified as an urgent imperative.[1]

“There is a clear need to develop and extend local clinical and epidemiologic research programs in developing countries which will result in acquisition of knowledge required to succeed in implementing preventive medicine programs,” write nine of the participants on behalf of the ISN-COMGAN Bellagio Study Group 2004.[2]

Such population-based research, leading to evidence-based public health practice, is the objective of three concurrent studies under way in Cuba.

“The studies represent a more developed stage in our emphasis on prevention, which has been a priority for us since the 1980’s,” notes Dr. Raúl Herrera Valdés, Director of the national Institute of Nephrology, a leading force in the three research projects.

Dr. Miguel Almaguer, head of the Institute’s Epidemiology Department, referred to earlier studies among samples in Pinar del Río, Camagüey, Cienfuegos and Santiago de Cuba Provinces, leading to the adoption of national prevention strategies in 1996. “But we realized we had to go deeper, and began designing the new set of research,” notes Dr. Almaguer, explaining that the team also received encouragement from Dr. Barry Brenner of Harvard, widely recognized as a world leader in preventive nephrology, during a visit to the island.

Dr. Herrera told MEDICC Review that the studies aim to identify, diagnose and study the behavior of CKD in differ-

“The studies are expected to reinforce and inform one another in pursuit of a nationally applied prevention program.”

—Dr. Raúl Herrera
ent Cuban populations; and then, combining these results with the international experience and recommendations, formulate primary and secondary prevention strategies that can be effectively implemented by the health system nationally. He emphasized that the three studies pursue similar aims, their more specific objectives and outcomes expected to both reinforce and inform one another in the pursuit of such a nationally applied prevention program.

On the ethical side, says Dr. Herrera, “it is important for us to guarantee access to nephrology services and renal replacement therapies for each new patient identified through the studies. In this regard, the extension of dialysis from 31 to 47 centers around the country, has offered us the backup we need.” (See Spotlight, this issue.)

The Studies

The Isle of Youth Study (ISYS): a longitudinal study in total population (80,721), expected to last decades, aspires to become the “Framingham of CKD” as Dr. Almaguer put it. The study contemplates the family as the essential unit for research. On the Isle of Youth, a family doctor tests patient’s urine sample following informed consent to participate in the study.

Phase I, involving community-based mass screening for markers of renal damage, began on November 1, 2004; by May, 2005, individual patient questionnaires, interviews and initial urine tests were expected to be completed, including those on newborns.[3] Early results show a 17-20% range for risk markers, according to Dr. Rafael Aguilera Copello, chief nephrologist on the Isle. “These are consistent with what we are also seeing in the Havana-Cerro study,” he told MEDICC Review.

Over the years, because of migration patterns to the southerly Isle of Youth, it has become a “genetic mosaic” of the Cuban mainland, reiterating its potential as an epidemiological guide, notes Dr. Aguilera Copello, local coordinator of the study. “The Isle of Youth,” comments Dr. Herrera, “also has the geographic and population proportions of many other island nations of the Caribbean, and thus the results of our research may be of particular importance to them as well.”

The study involves the Isle’s 113 family doctor-and-nurse teams, three polyclinics and municipal hospital (with nephrology services), which provide universal coverage there. The research is designed to:

- Identify main demographic and risk factors for chronic renal insufficiency and other chronic illnesses sharing vascular damage as a common denominator;
- Track these risk factors and patients over time;
- Identify persons with any degree of kidney dysfunction (through laboratory testing of the whole population, including proteinuria, hematuria, microalbuminuria, and serum creatinine);
- Track these persons over time, applying secondary preventive measures to slow the progress of their disease;
- Formulate and apply primary preventive strategies for those patients identified as healthy;
- Analyze the results of all stages of the study, and present the conclusions to national and international experts in the field.

At various stages, the study will branch out, to more profoundly examine areas of concern such as the relationship between CKD and cardiovascular or cerebrovascular disease, diabetes mellitus, hypertension, etc.

The Havana-Cerro Study: research among patients in the Cerro Municipality of the capital (total pop. 131,327) identified with risk factors for the development of CKD - some 30,000 persons,[4] The most immediate outcome of the study will be recommendations for comprehensive prevention and care models for such patients - commencing at the community level - to be piloted in Cerro. Leading the investigation is municipal health department director, Dr. Yamila de Armas, specialist in Family Medicine. She is joined by the 190 family doctors and nurses, four polyclinics and the Salvador Allende Teaching Hospital, which offer complete coverage to the population.

The study was begun in September, 2004 with the training of personnel; patient questionnaires, interviews and urine analyses were started in January, 2005, to be completed in the coming months. The key, notes Dr. de Armas, “is to design models of attention for these at-risk persons, from the family doctor on up to the tertiary level. We are looking at the way the patients flow through the system, building prevention into each level and each stage of illness, paying close attention to quality of care.”

“Our whole health system,” she emphasizes, “must be better organized around what our patients are getting sick from and what they are dying from; around this epidemiological evidence base. We are working to organize it logically, from the moment the patient enters the system - assessing what that patient requires at each level in terms of answers, resources and staff competencies. This study is invaluable because it synergizes this whole process, by giving us a concrete place to start.”

The Pinar del Río Study: research carried out in two of this westernmost province’s municipalities - Pinar del Río City and San Cristóbal - among approximately 43,000 persons identified with risk factors for the development of CKD. Part of the value added to this investigation resides in the difference between the two cohorts included - one located in an urban provincial capital, the other in a smaller, semi-rural moun-
tainous area (for more on San Cristóbal, see Bringing Services Closer to Home: MR Visits a New Dialysis Center in Cuba, this issue). Thus, results will offer additional comparative data to help complete the national picture of CKD, its risk factors and their relationship to genetic, environmental and other influences, as well as to other diseases rooted in vascular damage.

In addition, it is expected that initial epidemiological results from all three studies, particularly informed by the in-depth work on models of prevention-oriented care being formulated and piloted as part of the Havana-Cerro study, will allow Pinar del Río to be the first province to “scale up” the Cerro experience. The longer-range goal is to adapt and apply the models throughout the health system nationally.

The Pinar del Río study is now in the preparatory phase, under the leadership of provincial director of nephrology services, Dr. Leonel Soto, and testing is expected to begin before June 2005.

Prevention:
From Watchword to System-wide Practice

The studies aim for a precise characterization of the CKD epidemic in Cuba, with a more profound analysis of risk factors, both those known up to now and those that may be newly identified, “a first important step in public health policy planning,” notes Dr. Almaguer. Second, their results will inform the design of comprehensive models of education, prevention, and treatment at all levels of care. And third, it is expected that these models will be piloted, adapted and extended to the health care system as a whole. “This application in practical terms should become our most important contribution,” he says.

“We also hope this comprehensive approach will be a contribution to teaching, research, treatment and - above all - prevention in the region, says Dr. Herrera. “We believe that CKD can be used as a tracer, guiding prevention of other chronic conditions which have in common the same physiological mechanism of vascular damage. Preventive strategies designed and implemented for CKD should give us a vital head start on other critical health problems beginning to seriously burden developing countries like ours, including diabetes, hypertension, cardiovascular and cerebrovascular disease.”

References and Notes

[3] Dipstick urinalysis was performed initially on all participants, regarding as abnormal results of proteinuria \( \geq 1^+ \) and hematuria \( \geq 1^+ \). If test was negative for proteinuria and hematuria, then microalbuminuria dipstick urinalysis was performed in risk groups - including those with diabetes mellitus, hypertension, low birthweight antecedent, CKD family history, cardiovascular disease antecedent, pregnancy, obesity, renal disease antecedent, and in children \(<5\) years or persons \(\geq60\) years. Considered abnormal were results of microalbuminuria \( \geq 20 \) mg/L. All positive results for proteinuria, hematuria, or microalbuminuria are being studied for serum creatinine levels.
[4] The same definition of “at-risk populations” was used as for the ISYS study (see [3] above).
In Cuba, ‘no es fácil’ is a daily utterance. Still, ‘it’s not easy’ is an understatement for the 1800 Cubans who depend on life-sustaining dialysis to do the work of their kidneys. While the developing world’s health systems struggle with underreporting of kidney disease and increased end-stage renal disease (ESRD) mortality rates, Cuba’s universal approach adds another concern: how to get dialysis to everyone who needs it.

Imagine you live in the mountains, 125 miles from this life-saving service. To reach the dialysis center, you have to leave your house at four in the morning and take the bus into the nearest large city. Upon arrival, you wait for treatment, have your four hours with the machine and then get on the bus again, arriving home by midnight, if you’re lucky. This was the reality for hundreds of dialysis-dependent Cubans until 2003, when the Ministry of Health (MINSAP) launched a countrywide project to bring dialysis services closer to the people who need them.

In order to achieve this, a study was undertaken by government and the national Institute of Nephrology to analyze who needs dialysis services and where they live, how many more artificial kidneys were needed and where they would best be placed. Buildings and equipment were rehabilitated, built or bought, and medical and biomedical technical staff were trained; meanwhile, new centers were outfitted and existing ones upgraded – including the national Institute of Nephrology - a multi-million dollar investment. Now, some two years later, Cuba has 47 dialysis centers – up from 31 – spread across the country in locations designed according to patient need. Shorter travel times, better equipment and an integrated, creative approach to dialysis treatment, has meant improved quality of life for those with chronic kidney disease (CKD) and lower ESRD-related mortality rates.

Improving dialysis services and moving them closer to the patients who depend on them is one aspect of the Cuban health system’s strategy for managing renal diseases – reflecting the understanding that the island is not exempt from the international epidemic and its consequences. Indeed, the problem is on its way to worldwide crisis proportions: it is estimated that at least 60,000,000 people currently live with some degree of renal malfunction. Medical literature is unequivocal in its assessment of the alarming implications for health systems and the need for immediate action as regards prevention. Drs. Giuseppe Remuzzi and Jan Weening, leaders in the field, write: “Early detection of renal impairment, followed by preventive treatment, is...a global health priority...”[1]

In Cuba, three groundbreaking studies are in process, each designed to contribute to the formation and progressive implementation of comprehensive national strategies for prevention, early detection and continuous prevention-oriented treatment of renal disease. (See “Cuban Studies Aim for National CKD Prevention,” this issue). The urgency is also a product of rising life expectancy in Cuba, and the fact that people are living longer with such conditions as diabetes mellitus and hypertension.

On the day MEDICC Review visited the new dialysis center at the Comandante Pinares General Hospital in San Cristóbal, (easternmost Pinar del Río Province), the ward was a blur of green surgical scrubs as nephrologists and a six-member team of specialized nursing staff worked to change a life: a kidney had just arrived in Havana, and the staff moved to get their patient – who had been on the waiting list for a year – to the transplant center in time for her surgery. Cuba currently performs 22 kidney transplants per million inhabitants, a figure health officials here are expecting to increase.

**ESRD: Did You Know?**

- End-Stage Renal Disease is one of the most expensive chronic diseases to treat.
- Estimates for lifetime medical costs for an ESRD dialysis patient is US$253,000.
- Cuba has 1802 patients with ESRD in dialysis, or 160.8 per million inhabitants (March, 2005).
- Afro-Caribbeans may be 3 to 5 times more likely to develop kidney disease than whites.
- There are 1,800,000 known cases of ESRD across the globe.
- More than 1,000,000 worldwide receive dialysis; 90% of them are in North America, Europe and Japan.

**“Here, I don’t feel sick,” says Juan José Lorenzo, a 14-year veteran of dialysis treatment, pictured here with Dr. Cuesta.**
After the transplant patient had been safely whisked off to Havana and the bustle subsided, MR sat down with Dr. Orosman Cuesta, specialist in Nephrology and also Family Medicine, to talk about the new dialysis service in San Cristóbal, a small municipality of 64,000 people located at the foothills of the Sierra del Rosario mountains.

**MEDICC Review (MR):** Can you tell us a little about the history of this dialysis center?

**Dr Orosman Cuesta (OC):** The Hemodialysis Center in San Cristóbal opened one year and nine months ago with the purpose of bringing the services as close as possible to the homes of patients here in the province. Before, these patients had to travel around 200 kilometers [125 miles] to receive this treatment...in hospitals [in either Pinar del Río or Havana, depending].

The country originally had 31 dialysis centers and now we have 47. These aren't only in the provincial capitals, but reach all corners of the country, placed as close as possible to the population that needs them. An example of one of the farthest removed services from the provincial capital [to where patients had to travel previously for dialysis] is in Baracoa...in Guantánamo Province and in Sandino, here in Pinar del Río Province.

When our own new service started, with cutting-edge technology, it substantially improved the quality of life for these patients in terms of their integration into their jobs, their family and society. The patients themselves are more satisfied because not only do they receive treatment using the latest technology, but we have also offered them the chance of living in their own homes again [before, many had moved closer to the city or had long hospital stays there]. Mortality rates have also improved.

**MR:** How many patients are served by this center and how many dialysis machines do you have? How about your staff?

**OC:** This hospital extends dialysis services to patients from four municipalities (Palacios, San Cristóbal, Candelaria and Bahía Honda) throughout Pinar del Río, totalling 200,000 inhabitants. Right now we have 48 patients receiving dialysis here - 40 in hemodialysis and eight in peritoneal dialysis. We now have nine, quite modern artificial kidneys, and a state-of-the-art water treatment plant.

We have 48 people on staff. Of these, three are nephrologists, three are biomedical equipment engineers, 25 are nurses, and the rest are service workers, janitorial, cooking staff, etc. Ours is also an interdisciplinary team, linking the work of psychologists, psychiatrists, geriatric specialists, internists, nutritionists, and a nephrologist, who are in charge of patient care, guarantee nutrition, and provide dialysis services.

**MR:** How much does dialysis cost? Do patients have to pay?

**OC:** The service is free to patients, like other health services in the country. For a patient receiving three treatments a week, this costs the health system approximately US$12,000 to US$15,000 per patient, per year.

**MR:** Can you explain a typical treatment day for a dialysis patient before this center existed?

**OC:** These patients had to leave their homes at 4:00am, the bus would pick them up, and they would get to the dialysis center around 7:00. Frequently, because they had to wait their turn for a dialysis machine, they couldn't get home until 10, or 11 at night. The quality of life for these patients was practically nil. Many patients couldn't work, they lost ties with their family and were overwhelmed with the long distances they had to travel. After the remodelling, installing the new service, all of this changed. Not only has the treatment itself improved, but the program also guarantees adequate nutrition, with a daily protein quota. Furthermore, the transport brings them here at their appointed time for dialysis and takes them home when they finish. So the whole process, from when they leave home to when they get back, never takes more than six or seven hours. So in less than a workday, these patients are treated; they can go back to their lives and feel less of a burden. That's why we are especially pleased with the new program - we see our patients enjoying fuller lives.

**MR:** What happens if someone needing dialysis lives way up in the mountains and can't commute to the center?

**OC:** In spite of moving the services closer, there are still patients who live tucked away in the mountains or in areas that are difficult to reach, so we have casas de descanso [in San Cristóbal, this is a 16-bed facility where a handful of patients live during the week]. This guarantees them all the necessary comforts, with recreational activities, and staff that administers to them. And on weekends, they are given rides back to their homes. The house is also used for patients who don't have support or resources - people who are alone, without family or who need extra help. So it makes treatment easier, more accessible and of a higher quality. The other objective of the house is to provide continuing education not only in nephrology, but also in other related specialties including cardiology, endocrinology, geriatrics and training in how to manage other chronic, non-communicable diseases.

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MR INTERVIEWS

Roundtable with Two Generations of Cuban Nephrologists

By Michele Frank, MD, with MEDICC Review Staff

Cuban nephrology’s “founding fathers” sat down with the specialty’s new blood to discuss the history and trajectory of nephrology in Cuba, the importance of prevention, research and an integrated approach and what makes a good nephrologist. Convened by MEDICC Review at the national Institute of Nephrology in Havana, participating in the round table were Dr. Reynaldo Mañalich, Dr. Charles Magrans, Dr. Roxana Fraga and Dr. Christian Leyva.

Drs. Mañalich and Magrans, both nephrologists, professors and researchers, are two of the specialty’s pioneers in Cuba, while Drs. Fraga and Leyva are residents-in-training for what will be their second specialty, since both completed residencies in family medicine and worked as community-based primary care physicians before coming to the Institute. Given the presence of two of the architects of modern Cuban nephrology, we took the opportunity to begin by talking a little about the specialty on the island.

MR: How has this specialty been able to integrate the changes in focus that have come about as the Cuban health system has evolved? Historically how have these changes developed and what role does prevention play?

Dr. Magrans: During the early years of the revolution [1960s, eds.], a working group was set up to try to begin to provide dialysis for the whole country...Initially three groups were established – one in the eastern part of the country, one in Villa Clara in central Cuba and one in Havana – all trying to develop ways to deal, primarily, with the problem of Acute Renal Failure (ARF) and its consequences, and kidney disease in general.

We were internists, internal medicine specialists, not nephrologists. Nevertheless, we began to dialyze patients and to treat ARF. By 1961 or 1962, we began to realize that our biggest challenge wasn’t treating ARF, but rather preventing it - preventing renal disease and other, often underlying, pathologies which lead to Acute Renal Failure...In order to be able to do prevention, we had to delve deeper into causes - sepsis for example. This is how nephrology as a specialty began to develop, and we were always pushing ahead, aiming to organize ourselves and the work better...One of the most important contributions made by Dr. Buch [founder and first Director of the Institute of Nephrology, Honorary President of the Latin American Society of Nephrology and the Cuban Society of Nephrology, eds.] was his extraordinary ability to motivate the people who worked with him. And I’m not just talking about other doctors, but also nurses, technicians, the whole group – we were very, very integrated and dedicated and we worked day and night – it was intense and the level of commitment was extraordinary.

We began to think, next, about the importance of training nephrologists in Cuba. So by the end of the 1960s, we were looking for ways to improve the training, improve the curriculum and just generally upgrade the whole specialty. Also, up to that point, nephrology-as-a-specialty was basically a matter of services for patients with acute disease. Then we began to work with chronic patients - fundamentally using periodic dialysis and beginning to look into renal transplantation.

In 1968, the Ministry of Public Health designated two people to study nephrology as a specialty in its own right. We put together a curriculum, a training program, based on visits we had made to other countries and on international exchanges that were taking place - with France, for example. So this is how our first specialists were trained. This quickly led us to begin thinking much more seriously about transplantation, especially now that we were having such positive results keeping people alive with dialysis. The first Cuban kidney transplant took place on February 24, 1970 and we were tremendously lucky because everything turned out well, the results were good; it was a successful transplant. That year we did 14 transplants.

MR: Your generation really created the Cuban “school of nephrology.” What have been the most important models and contributions to this effort, both nationally and internationally?

Dr. Mañalich: From my point of view, there are several key “moments” or elements that are particularly important. One of these is that Dr. Buch, Dr. Magrans and myself had the opportunity in 1957 to take part in a very significant event that was Dr. Willem Kolff’s visit to Cuba. Dr. Kolff, a physician from Holland, was the creator of the first artificial kidney and he gave a very important presentation here at the hospital where the Institute is now located. Also very significant in relation to the development of nephrology in Cuba was the assistance and collaboration offered by Dr. Jiří Jirka of Czechoslovakia – he was instrumental in helping to build the foundation of what would become our specialty, [introducing] us to a much broader view and scope of nephrology, beyond just dialysis and transplants. The other important aspect is the role that Dr. Buch played in all of this. Because of him, I believe, we were able to capture the attention of the Ministry of Public Health and the Minister at that time, who was Dr. Ramón Machado Ventura. Dr. Machado Ventura had phenomenal vision - for example, he created the research institutes of the Ministry of Public Health, including the Institute of Nephrology - with just three people!
Back then, at the very beginning, our patients came from all across the country because there wasn’t any other place where they could get dialysis…The amazing, and perhaps most important, thing about all of this - thanks to Dr. Buch’s vision - is that the development of nephrology in Cuba was not limited to the Institute. He worked hard to extend these services to other hospitals in Havana and also to the pediatric hospitals. It was with pediatrician Dr. Santiago Valdés Martín’s participation that pediatric nephrology was born in Cuba.

So, nephrology reached other hospitals, other provinces, right from the beginning, and the numbers of nephrologists have been growing steadily. Right now, there are 280 nephrologists and 150 residents in training throughout the country.

I guess you could say that we were the seeds – it started here with us - but it grew and developed rapidly because of what I like to call “the Buch principle” which was the principle of “universalization” of the specialty. He had a very clear vision in this regard and pushed for it. This, of course, dovetails very well with Cuba’s commitment to universal health coverage. Now our challenge is to continue to broaden dialysis and transplant opportunities, to expand and further develop access throughout the country, and to thoroughly research the current health status of the population in this regard, to do an accurate needs assessment.

Dr. Magrans: I think the first fundamental concept is this idea, from the very beginning, of the “universalization” of care - that it should be available everywhere, to everyone in the country…But preventing Acute Renal Failure (ARF) from developing in the first place is the most serious and important task before us.

MR: How does organ donation work in Cuba? Is there an organ donor program?

Dr. Magrans: Organ donation has involved education mainly - an educational process guided by strict ethical principles. In the first place, this is considered a family decision, the family has to authorize it. At one time we actually had an organ donor program like some other countries where people registered so that their identification papers indicated they wanted to be donors, in case of an accident or whatever. This kind of thing isn’t so necessary any more here because people are much clearer on the issue - it has become almost a cultural thing, something natural or normal, whereby families just generally accept the idea of organ donation as a good and positive thing…Here in Cuba family members will donate an organ if it will save a life, if there’s compatibility. The majority of the kidneys used for transplant come from accident victims, and about 10% from relatives.

MR: Turning to the younger generation, as residents here at the Institute, what are some of the things that have most impressed you about your professors?

Dr. Fraga: From the very beginning what I noticed most was how the professors are so committed, so intent on transmitting to us a sense of unconditional dedication…They have dedicated their lives to the development of this specialty in our country, but in addition they have been able to inspire us to feel great love for the work, for the patients, for the specialty. We understand that this specialty requires a great deal of sacrifice, dedication, scientific excellence, and passion - lots of passion!

Another thing that has had a big impact on us, I think, is that our professors have always tried to make sure that we understand the importance of being well-rounded, of being ‘integral’ or ‘integrative nephrologists’ - meaning that we should be able to do everything, participate in, and understand, everything. We are being trained to be nephrologists who can look into a microscope, analyze a biopsy and together with the pathologist, present the diagnostic discussion; nephrologists who can be with a patient receiving hemodialysis and know all about everything that’s going on with the artificial kidney, including the mechanical or technical aspects; and, of course, we also are trained to know and understand which elements of a particular situation are important in terms of prevention, to understand risk factors.
The preventative approach is something we ourselves bring to the specialty: we know a lot about the base, the community, and how to analyze health situations with an eye to prevention, because we were family doctors before coming here. [Virtually all Cuban physicians must first complete a residency in family medicine before going on to a second specialty, eds.]. We understand how to look for risk factors and how important this can be. There has been a notable rise in kidney disease: we need to understand this better, we need to go out into the community and pro-actively look for risk factors and study incidence.

Finally, I would say that our professors have been really great about helping us find good bibliography so we can really study and keep up-to-date in terms of the medical literature in our field. This is important in any field of medicine, but I think in ours especially, because of both this rise in incidence on the one hand and the need for new or innovative approaches on the other.

**MR:** What do you think Cuba’s role or contribution should be internationally to the field of nephrology, particularly for other developing countries?

**Dr. Leyva:** I think the most important contribution Cuba has to make is related to our preventive focus, given the particular characteristics of the Cuban health care system. Perhaps we do not have the most advanced technology or diagnostic equipment, for example, but with regards to prevention programs, early diagnosis, the “universalization” of health care delivery...in these aspects, I think we have something special to offer the international community. In fact, we are carrying out a major research project in this respect. It’s taking place on the Isle of Youth and perhaps from this we will be able to develop something that will not only benefit Cuba but that will be our contribution to the world. [For more, see “Cuban Studies Aim for CKD Prevention,” this issue.]

**MR:** What does it take to be a good nephrologist?

**Dr. Leyva:** In the first place, to be a good nephrologist, you have to be a good doctor. Nephrology involves all aspects of medicine - from the psychological to the organic. So the first and most important thing is, you have to be a good doctor. And not just from the point of view of the kidney: you need to study cardiology, psychology, etc. For example, the first to confront the problem of depression of the immune system were nephrologists, yet this is something that is apparently outside our area of expertise, but in fact that’s not the case. And there are a number of areas like this. You have to be able to integrate knowledge, to think! Thinking, analysis, the process of thinking things through and integrating information and knowledge, are fundamental to becoming a good nephrologist.

**Dr. Fraga:** I think it’s key to understand the importance of all aspects of nephrology. I mean, the prevention aspects are just as important as a timely diagnosis, for example, which is just as important as the treatment plan and adequate follow-up. You want to guarantee that hemodialysis goes well, you want to ensure the best possible preparation of the patient who is going to have a transplant...and then follow-up is very important too. Just like every patient should be given equal, totally dedicated attention: it’s what they deserve, it’s their right.

**Dr. Magrans:** I think this specialty has a particular characteristic in that it permits you to help patients continue to live, it’s a specialty that can keep people alive, for years even. The kidney as an organ is very important in this regard and the fact that we can maintain those functions, even artificially, is one of the things that gives nephrology its special and unique character.

For example, in Cuba the latest statistics indicate that 111 patients per one million inhabitants begin dialysis last year. We see them constantly, continuously, so we become like one big family...Imagine a patient who comes in for dialysis for four hours, three times a week over the course of, say, 10 years. This is a relative! This is a family member for all the people who work here. This is what makes for the human part of this work; it leaves it’s mark, believe me...The chronic patients nourish our humanity, they sensitize us in a way that makes us want to work more, dedicate more time, more energy, more effort...This is what I think is the mark of a good nephrologist. You see these patients, these people, you treat them, and the humanitarian aspects are what motivate you. It generates interest and a desire to study more, learn more – to try to resolve the problems. I think this is a characteristic of our public health system in general. So you think in human terms. For example, you worry about the cardiac patient, or any patient, not having to be transported great distances, being able to be closer to home...bringing health care as close to where people live and work as possible, into their communities, this is a general concern and responsibility throughout the public health system. [See “Bringing Services Closer to Home: MR Visits a New Dialysis Center in Cuba,” this issue.]

**Dr. Mañalich:** And looking at it from yet another angle, it seems to me that good nephrologists should be good specialists in internal medicine, or good pediatricians. Nephrology relates to all the body’s systems and you have to be knowledgeable in terms of liver disease, heart, lung, the brain...You have to have an integral approach and profound knowledge of many, many aspects of medicine, whether it’s endocrinology, immunology or cardiology. The nephrologist needs to be well versed in all of these because you can’t be sending the patient off to this specialist and that specialist. The patient isn’t a sum of different little parts with each part receiving separate, isolated attention from different medical specialists. It doesn’t work, in my opinion, in any setting, but in nephrology it definitely doesn’t work. To be a good nephrologist, you have to be able to see the whole patient, the whole person.
Specialists gather this month in Cuba for the 9th Central American and Caribbean Congress on Nephrology and Hypertension, to coincide with the 3rd International Meeting on Nephrology Nursing and Cuba’s own 7th National Congress on Nephrology.

Dr. Jorge Alfonzo, President of the Cuban Society of Nephrology, told MEDICC Review that prevention of chronic kidney disease is the main focus of the event, which has attracted participants from the region, as well as Europe, North and South America, and Asia.

Some 400 Cuban and 250 international physicians, nurses and other health professionals whose work is related to renal disease are expected.

In keeping with the main theme, the Congress opens with the lecture “A Global Perspective on Kidney Disease: Implications for Central America and the Caribbean” by Dr. John Dirks, Chair of the International Society of Nephrology’s Commission for the Global Advancement of Nephrology (COMGAN), from the University of Toronto.

Central America and the Caribbean are comprised of 34 countries, with 76 million inhabitants. Over 40% live in poverty. Communicable and non-communicable diseases both have significant impact on morbidity and mortality, and chronic disease prevalence is projected to increase with current aging trends of the population. Obesity is at epidemic levels among the near-poor. Prevalence in total population of diabetes mellitus is 6%-8%; and hypertension 8%-30% - although both conditions are certainly under-diagnosed in almost all countries.

The region’s racial-ethnic composition - associated with difficult socio-economic conditions - can be compared to U.S. minorities, which show significantly greater rates of CKD than those registered in Central America and the Caribbean. Thus, the region may well be among the world’s most seriously threatened by CKD – a reality obscured by the lack of health care coverage and consequent underreporting, as indicated by an excessively low prevalence of patients in dialysis. The most recent data from the Latin American Registry (2001) indicates that, except for Puerto Rico, the incidence of chronic patients in dialysis in Central America and the Caribbean is 60 pmp or fewer, and prevalence in dialysis is fewer than 100 pmp. Several countries have no program for renal replacement therapy.

As with other developing countries, says Dr. Alfonzo, “prevention is our best hope in the region for stemming the tide of chronic kidney disease, and other conditions associated with it.”

The Congress Agenda

Prevention at all levels of healthcare is an underlying theme guiding the work of the entire Congress as it focuses on such areas as:

- Nephrology in primary care
- Teaching nephrology
- Quality of life for patients in dialysis and transplant patients

The main sessions (May 15-18) are preceded by several pre-Congress courses:

- Prevention and Progression of Chronic Renal Insufficiency, opened by Dr. Jan Weening, President of the International Society of Nephrology (ISN) and led by Dr. John Dirks, Chair of the ISN’s Commission for the Global Advancement of Nephrology (COMGAN) from the University of Toronto. (Sponsored by the ISN and COMGAN).

- Hypertension and Vascular Risk Associated with Chronic Kidney Disease, directed by Dr. José Luño, Hospital General Universitario Gregorio Marañón, Madrid. (Sponsored by the Spanish Society of Nephrology).

- Nephrology Nursing Update, opened by Dolores Andréu Periz of Spain and Migdalia Delgado Miranda of Cuba. (Sponsored by the Spanish Society of Nurses in Nephrology, the Mexican Association of Nurses in Nephrology, and the Cuban Society of Nursing).

- Pediatric Nephrology Update, led by Dr. Santiago Valdés Martín, Centro Habana Pediatric Teaching Hospital, Havana. (Sponsored by the Latin American Society of Pediatric Nephrology, the Cuban Society of Pediatrics and the Cuban Society of Nephrology).
CUBAN MEDICAL LITERATURE

Effect of Primary Health Care on Prevention of Chronic Kidney Disease in Cuba

By Miguel Almaguer López, MD

INTRODUCTION

Chronic kidney disease (CKD) is an important and increasing health problem in the world and also in Cuba. Epidemiologic research has demonstrated that there is an increase in incidence, prevalence and complications of this disease. Its progression towards end-stage renal disease (ESRD) has caused a yearly exponential rise in new patients requiring renal replacement, such as dialysis or renal transplant, from 7% to 10%, depending on the country.[1] In addition to the ethic, economic, and social effects on health services and society, this creates significant human suffering for the patient and his family.

There is growing evidence regarding effective interventions for preventing CKD and its progression, which could potentially bring about a decrease in the complications, the need for dialysis or renal transplant, and premature death.

In Cuba, measures are being introduced - mainly at the primary health care level - with the purpose of reducing CKD and its complications in the general population.

NATIONAL HEALTH SYSTEM AND PRIMARY HEALTH CARE

Cuba has a population of 11,250,979 inhabitants and a land surface of 110,922 sq km. The country has a unique public health system, which is free and accessible to the entire population. It includes 67,079 doctors, 31,059 of whom are dedicated to primary health care.[2] Primary health care includes 444 territories called health areas, each one having an outpatient clinic and a variable number of family doctor’s offices depending on its total population. Each family doctor treats an average population of 120 families, or around 600 people.

Some of the country’s main health indicators are: an infant mortality rate of 6.5 deaths per 1000 live births [rate for 2004: 5.8 X 1000, eds]; 99.2% of the children are alive at 5 years of age and 95% of children receive a complete vaccination schedule against thirteen preventable diseases [rate for 2004: 98%, eds]. Life expectancy is over 75 years for both sexes and only 1% of total deaths are due to infectious diseases. The main causes of death are cardiovascular diseases, cancer, cerebrovascular diseases and diabetes mellitus, among other non-communicable diseases.[2] CKD appears in this public health context.

CHRONIC KIDNEY DISEASE BURDEN

The first national primary CKD mortality study was carried out from 1970-1972. It was based on death certificates and autopsies performed in hospitals showing 89% of diagnoses confirmed through anatomical pathology. A death rate of 101 to 132 per million inhabitants was found.[3] In 1991, a national study of multiple death causes from chronic renal failure was carried out. It was based on death certificates, which defined the main causes of CKD as: diabetes mellitus 30.5%; arterial hypertension 19.8%; urological causes 9.8%; glomerulopathies 7.3%; and congenital, 5%.[4]

Several population-based epidemiological studies during the 1984-1992 period have described a prevalence of chronic renal failure of 1.1 to 3.5 patients per 1000 inhabitants.[5,6,7]

A population-based screening and follow-up study with intervention during nine years of primary health care in 627 patients with glomerular filtration rates (GFR) <70 ml/min, showed a change in the distribution of patients according to stage of CKD. At the beginning of the study, 37% of the patients had GFR of 70-30 ml/min and by the end, it rose to 76%.[5]

NATIONAL PROGRAM FOR PREVENTION OF CHRONIC KIDNEY DISEASE

In 1996, the Ministry of Public Health approved the National Program for the Prevention of CKD,[8] which forms part of the National Program for the Prevention of Non-Communicable Diseases.

The objectives are a reduction of CKD risk factors in the general population, identification and monitoring of individuals at increased risk for developing CKD, early CKD diagnosis and effective treatment to delay its progression. Additional objectives include patient rehabilitation and improvement in quality of life, and establishment of a CKD surveillance system at the primary health care level.

The program considers interventions at the level of general population and among individuals; the cornerstone of this strategy is the family doctor interacting with nephrologists at the primary health care level (see Figure 1).

PROCEDURE FOR IMPLEMENTING THE PROGRAM

Several steps have been taken for the progressive implementation of the program. The main ones are described below.

The first step, already described in its initial phases, is the epidemiological study of the disease burden, its patterns, distribution and trends, and a small-scale trial of the interventions.

A second important step is the training of the health team performing the interventions at the primary health care level. Improving the knowledge base and competencies of the health team, guided by the goals of the program, is essential.
Nephrology residents’ curriculum includes a subject called “Community-Based Preventive Nephrology.” Family doctors receive a 40-hour course on “Prevention, Diagnosis and Treatment of Chronic Kidney Disease,” taught by nephrologists at outpatient clinics (primary health care). Furthermore, there is a longer 400-hour course on “Preventive Nephrology” for family doctors selected by each clinic.

A third step is redirecting services for nephrology patients towards primary care institutions, bringing them closer to the community.

A fourth step is the inclusion of CKD in the continuous assessment and risk evaluation (CARE) system carried out by family doctors and nurses (registry, risk evaluation, treatment, vaccination against hepatitis B virus and follow-up with the patients by family doctors). Patients with diabetes mellitus and high blood pressure (HBP), both substantial in groups with increased CKD risk, are also included in the CARE system, contributing to better monitoring of these risk groups.

The CARE system, together with other information sources of the national health system, integrates the CKD surveillance system into primary health care.

Another important step are the actions directed at health promotion in the general population, taken by the health and other sectors, which contribute to CKD prevention.

RESULTS

The CKD Prevention Program, integrated into the Program for the Prevention of Chronic Non-Communicable Diseases, has achieved the following results in accordance with the objectives of the program.

Risk for CKD has been reduced in the general population. Smoking prevalence, 36.8% in 1995, dropped to 31.9% in 2001;[9] control of HBP > 149/90 mmHg in patients with hypertension, 45.2% in 1995, rose to 52.0% in 2001;[9] and low birth weight, 7.9% in 1995, decreased to 5.9% in 2002.[2] Vaccination against hepatitis B (HBV) in initial stage CKD patients at the primary health care level and at the dialysis centers reduced HBV incidence to 0.1% in 2002.[10]

To bring services closer to the community, nephrology departments in the country were increased from 31 to 47, with significant increase in dialysis capacities. Nephrology departments and related primary health care territories were re-distributed. New nephrology outpatient services were opened at the primary level. This increases the interaction of nephrologists and family doctors, making the referral and cross referral of CKD patients easier.

CKD prevention training of the primary health care team has improved diagnosis and treatment; 841 family doctors have received the 40-hour course on prevention, diagnosis and treatment of chronic renal disease and 128 family doctors passed the 400-hour preventive nephrology course.

Numbers of known diabetes mellitus and HBP patients registered by family doctors have risen. Prevalence of known diabetic patients was 18.1 per 1000 inh. in 1995 and 27.1 per 1000 inh. by 2002.[11] Prevalence of known patients with chronic renal failure, serum creatinine level ≥133 mmol/L (≥1.5 mg/dl), also rose from 0.61 per 1000 inh. in 1995 to 0.92 per 1000 inh. in 2002.[11]

The registry and follow-up at the primary health care level of patients with increased CKD risk and patients with chronic renal failure is one of the elements of the CKD surveillance system, which, together with other information sources available in the health system, has enabled knowledge to be gathered on the frequency, distribution patterns and trends of the disease in the population and the program’s actions to be evaluated.

CONCLUSIONS

1. The CKD Prevention Program is being implemented and extended in primary health care centers across the country.
2. Program actions are carried out in an integrated manner with other programs of the health sector and other sectors.
3. Nephrology departments have moved closer to the community, improving referral and cross referral of patients with CKD.
4. There is improved knowledge and competencies among family doctors for carrying out CKD prevention in primary care.
5. CKD risk in the population has decreased; there is reduced smoking; decreased low weight births; greater control of HBP; and decreased incidence of infections from hepatitis B virus in dialysis patients.

6. The number of diagnosed patients with diabetes mellitus and HBP registered by family doctors in primary care has increased.

7. The number of diagnosed patients with chronic renal failure registered by family doctors in primary health care has increased.

8. Primary health care and the community are the public health tools and ideal social space for carrying out health promotion and the prevention of CKD.

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CUBAN MEDICAL LITERATURE

Hypertension in Children: Diagnosis and Treatment for Renovascular Hypertension over a 15-Year Period

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ABSTRACT

Forty five hypertensive children age 2-18 with at least one possible clinical sign of renovascular hypertension (RVH), were enrolled in a screening program for diagnosis and treatment of RVH over a 15-year period at the national Institute of Nephrology. The mean age was 14.7 +/- 3.78 years, with 21.5 +/- 26.6 months of known hypertension. Mean systolic blood pressure (SBP) was 163.9 +/- 21.7 mmHg and diastolic blood pressure (DBP) was 115.4 +/- 20.8 mmHg. Patients underwent a variety of biochemical and imaging studies, but in all cases, renal arteriography was used to determine the precise diagnosis and treatment strategy. Sixteen children (35.6%), were identified with renal artery stenosis, 11 unilateral (68.7%) and 97% due to fibromuscular dysplasia, four cases (8.9%) with longitudinal narrowing of the renal artery with an atrophic dysfunctional kidney, one case (2.2%) with intra-renal angioma, one (2.2%) arteriogram not useful in defining artery disease, and in 23 patients (51.1%), the study was normal. Three therapeutic modalities were chosen: medical therapy with antihypertensive medications, percutaneous transluminal angioplasty (PTA) and surgery (autotransplant or nephrectomy). The aim of treatment was BP control and renal function preservation. In 43 children (95.6%) BP was normalized, 31.1% of these were completely cured and 64.5% improved with additional medical treatment. All RVH cases treated by surgical procedures were cured. PTA was successful in eight patients and in two other cases PTA was combined with surgery. Blood pressure was normalized in 70% of cases treated by PTA. Two patients were lost to follow-up and the remaining 26 non-RVH children (57.8%) were treated with long-term antihypertensive medications; all of these had adequate BP control and normal renal function.

Keywords: HYPERTENSION, CHILDREN, RENOVASCULAR HYPERTENSION, PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY
INTRODUCTION

Hypertension is not common in children.[1] Although it is generally agreed that early essential hypertension poses little immediate risk to most children, evidence from preliminary studies of children and adolescents has shown hypertensive heart disease and hemodynamic changes consistent with an adverse effect of mild hypertension before the third decade of life.[2-8] Secondary hypertension is more common in children than in adults and can lead to organ damage and increased mortality.[8] The cause is multifaceted, but renovascular hypertension (RVH) is an important cause of secondary hypertension in children accounting for 5% to 25% of cases.[5,7,8] The exact prevalence of RVH in children is unknown. The most common cause is fibromuscular hyperplasia,[5-7,9-11] Other identified associated causes are coarctation of the aorta, different types of arteritis, neurofibromatosis and idiopathic hypercalcemia (Williams-Bueren syndrome).[3,6]

We present a retrospective study in a population of hypertensive children with clinical suspicious signs of renovascular hypertension. The aim of the study was to evaluate a number of pediatric patients with hypertension during a 15-year period (1986-2000), and in so doing, make an early diagnosis of RVH and subsequently examine three separate therapies. We describe clinical, laboratory and radiological findings, management and patient outcome.

MATERIALS AND METHODS

Patients

All hypertensive children age 2-18 referred to the hypertension clinic of the national Institute of Nephrology, were eligible for inclusion. All had at least one possible clinical sign of RVH (severe hypertension exceeding the 99th percentile for age and sex; resistance to antihypertensive medications; responses to ACE inhibitors; systo-diastolic peri-umbilical noise; or hypertensive encephalopathy), at the time of enrollment into a screening program for diagnosis and treatment of RVH from 1986 to 2000.[11] Hypertension was defined as systolic and/or diastolic blood pressure persistently above the 95th percentile for age, sex and height[1] for patients up to the age of 16; for those between the ages of 17 and 18, it was defined according to the WHO (>140/90 mmHg) regardless of gender.

Screening Test

A complete clinical examination, hematology, biochemical screening test, urinalysis, imaging studies, and peripheral and separate renal venous plasma renin activity (PRA) was obtained.[11,12] In addition, captopril-stimulated plasma renin tests were obtained in all cases (patients did not receive any antihypertensive medication for at least two weeks and were not salt depleted). The test was performed in the morning in fasting sitting position. After a 30-minute rest period in the supine position, a single dose of captopril 0.63+0.05 mg/kg body weights was given. Blood sampling was collected before and 60 minutes after dosage for determination of plasma renin concentration (normal range 1 to 2.70 ng/ml/hr). Blood pressure was measured 10, 20 and 30 minutes before captopril administration to get baseline BP and every 15 minutes during an hour. PRA was measured by radioimmunoassay using a commercially available kit. According to the criteria of Muller et al. and Alfonzo et al.,[11] the captopril test was positive if the post-captopril PRA (ng/ml/hr) was greater than 12, with an increase of e°10, and a relative increase of e°15% (400% if initial PRA was <300). Measurement of renal vein renin levels was used to confirm the hemodynamic significance of confined renal artery stenosis. Ratio of <1.5:1 was considered significant and predicted a positive response to revascularization or nephrectomy for atrophic non-functioning kidney.

99mTc-diethylenetriaminepentaacetate (Tc-99mDTPA) or 99mTc-mercaptoacetyltriglycerine-MAG3 (Tc-99MAG-3) scintigraphy basal and post-captopril study were performed during the screening period in basal condition and one hour after oral administration of Captopril.[3,13] Images were obtained by means of a gamma camera (GE 400 AT) equipped with general purpose collimator after an intravenous injection of radio-nuclide. Each scintigraphic study was interpreted visually and according to renogram curve patterns. Semi-quantitative parameters (Tmax mean transit time, relative renal function (%) and renal output efficiency), were also calculated.[2,11,13,14] A scintigraphic study is considered pathological if the curve shows a delay peak (beyond six minutes Tmax) or there is an asymmetric renal function (>60% or <40%). Subtraction aortorenal arteriography was performed in all cases (RVH significant stenosis >60% of lumen reduction), and selective renal arteriography pre and post PTA. The etiology of fibromuscular disease or arteritis was classified on the basis of the angiographic appearance as defined by McCormack LJ et al[15] in the absence of diabetes, neurofibromatosis, Takayasu arteritis atheromatosis of the aorta and its major branches, and young age of the patients. No material was available for histological analysis, except the atrophic kidneys after nephrectomy.

Patient Follow-Up and Endpoints for Treatment

Patients were seen at 1, 3, 5 and 10-year intervals in an outpatient setting after discharge from the hospital or initiation of drug therapy. During the remaining time, their pediatric or primary care physician followed the patient clinically and monitored medication dosage. The endpoints for treatment in all cases were: 1) blood pressure (BP) control, 2) serum creatinine as measurement of renal function, 3) the date of inclusion in a dialysis program or rise in creatinine to 4.5 mg/dl and 4) patient survival.

Therapy

Utilizing this array of procedures, we defined anatomical and functional status of renal vasculature in order to be guided towards the most appropriate therapeutic option. Once diagnosis was established, three therapeutic modalities were chosen: 1) medical therapy with antihypertension drugs in non-RVH patients, patients awaiting angioplasty or revascularization, and those who have failed to respond to intervention, 2) percutaneous transluminal angioplasty (PTA) was our first choice for main trunk disease, 3) surgery revascularization or autotransplant in patients where PTA fails and for those beyond the first bifurcation intrarenally involving branched arteries stenosis, 4) removal of a completely atrophic dysfunctional kidney with high renal vein plasma renin activity or 5) a combination of PTA and surgery.

Statistical Analysis

Data were described as frequencies, medians with ranges and means with standard deviation (SD), as appropriate. Two-by-two contingency tables were analyzed using the chi-square test or in the case of small numbers, Fisher’s exact test. P<0.05 was set as the level of statistical significance.
Results

Medical records were reviewed from a consecutive series of 45 hypertensive children (16 RVH and 29 non-RVH), 17 females and 28 males (Table 1). The mean age of the population was 14.7 +/- 3.78 years (range from 2-18 years). Twenty-eight patients were Caucasian, while 17 were Afro-Caribbean. The duration of known hypertension was 21.3 +/- 26.6 months (ranging from 1-120 months). At the time of their first medical visit, blood pressure (BP) was 163.9 +/- 21.7 mmHg for systolic and 115.4 +/- 20.8 mmHg for diastolic. Almost all patients had a few symptoms (headache, palpitation, flushing, etc). Mean serum creatinine level was 0.86 +/- 0.20 mg/dL and mean plasma renin activity was 7.6 +/- 6.4 ng/ml/hr. Captopril-stimulated plasma renin activity tests were positive in 63% (76% in RVH and 52% non-RVH) (p<0.05) of children in which they were performed. In our series, basal and post-captopril scintigraphy was positive in 69.2% of RVH cases, and in only 23.5% of non-RVH patients (p<0.05). Non-statistical significance level was found between RVH and non-RVH patients in age, sex, gender, mean systolic blood pressure, mean serum creatinine plasma activity and measurement of renal vein renin levels. Statistical significance (p<0.05) was found in all cases of known hypertension, diastolic blood pressure, Captopril scintigraphy test and Captopril plasma renin activity test. (Table 1). Digital subtraction arteriography demonstrated 16 renal artery stenosis (35.6%), 11 unilateral (22.2%) and 5 bilateral (11.1%), four cases of longitudinal narrowing renal artery (8.9%) without a specific stenosis with a reduced kidney size (atrophic or hypoplasia), one case (2.2%) with renal angioma, one arteriography (2.2%) which was not useful in defining artery disease for technical reasons, and in 23 patients (51.1%), the study was normal. Extra renal lesions (aorta, mesenteric or cerebral) were not found, although no systematic study was done for this purpose.

The etiology of hypertension in our series was: renovascular hypertension (artery stenosis >60%) 16 cases (35.6%) and non-RVH 29 patients (64.4%). Non-RVH etiologies: four cases related to longitudinal narrowing renal artery without stenosis with a reduce kidney size (8.9%), 1 patient with renal angioma (2.2%) an in other 29 patients (53.3%), non-other causes of secondary hypertension were not identified (essential hypertension).

Once the diagnosis was established, three therapeutic modalities were chosen: medical therapy with antihypertensive drugs (28 non-RVH patients), PTA (10 RVH patients) and surgery (seven cases - 6 RVH and one non-RVH patient). Percutaneous transluminal angioplasty or surgery was used in 17 patients (37.8%) - 16 RVH and one non-RVH. PTA (without stent placement, our first choice) was performed in eight cases (17.8%), six unilateral and two bilateral. PTA plus surgery (PTA and autotransplant in a bilateral stenosis case and one nephrectomy after PTA thrombosis) was used in two cases (4.4%) and a surgical procedure alone (four nephrectomy in completely atrophic dysfunctional kidney with main branch artery stenosis, a nephrectomy in one non-RVH patient with an atrophic kidney, one pheochromocytoma resection in the renal hilium with direct arterial compression and one partial nephrectomy for an angioma), was used in the remaining seven patients (15.6%). Twenty-eight non-RVH patients (62.2%), received medical treatment only (beta blocker, calcium antagonist, ACE-inhibitors and diuretics). We avoid the use of ACE-inhibitors or antagonist receptors of angiotensin in RVH patients because they can induce renal dysfunction in cases with bilateral stenosis or in a solitary functioning kidney. At the end of the follow-up period, 43 patients (95.6%) were normotensive, 14 (31.1%) of them without the use of antihypertensives and 29 (64.5%) with antihypertensive drugs. Two children (4.4%) were lost to follow-up. (Table 2). Of the 16 RVH patients, 12 (75%) were normotensive without antihypertensive drugs after PTA or nephrectomy. In three (18.75%) BP was normal but needed some drug support and one case was lost of follow-up.

In all cases treated with a surgical procedure, complete control of the BP was obtained (five RVH and two non-RVH patients). PTA alone in RVH patients was successful in eight cases; in two other cases, it was successful when combined with surgery (one autotransplant and one nephrectomy). In seven patients (70%), the high blood pressure was cured, while three patients (30%), required some form of medication to control blood pressure, albeit in a small dosage. Mean serum creatinine levels were maintained within normal limits during all follow-up periods. The only case with abnormal basal serum creatinine and treated with antihypertensives was stable after five years of follow-up. There was not mortality in the study.

Renovascular Hypertension Patients

In this study, 16 patients, 10 males (62.5%) and 6 females (37.5%) were identified as having RVH secondary to renal artery stenosis, 11 unilateral (68.7%) and five bilateral (31.3%) (Table 1). The prevalence of RVH in our series is 35.6%. Fibromuscular dysplasia accounted for 11 cases (68.7%), and the etiology of the other cases was: three arteritis (18.7%), one hiliar pheochromocytoma with direct arterial compression (6.3%) and one unclassified arterial disease (arteritis?) (6.3%). Ten of these cases were treated by PTA. In eight patients, PTA alone without stent was employed (median age 14.8 years, six with unilateral stenosis). Blood pressure was normalized in five patients (62.5%), and improved in three (37.5%) with drugs, albeit in a small dose,

Table 1: Baseline Clinical and Laboratory Findings in 45 Hypertensive Patients Aged 2-18 Years, Institute of Nephrology, Havana, (1986 – 2001)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RVH n = 16</th>
<th>NON-RVH n = 29</th>
<th>Total Number n = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (62.5%)</td>
<td>18 (62.8%)</td>
<td>28 (62.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (37.5%)</td>
<td>11 (37.19%)</td>
<td>17 (37.19%)</td>
</tr>
<tr>
<td>Time of known hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(months)</td>
<td>7.6 +/- 6.7</td>
<td>55.6 +/- 56.1*</td>
<td>63.1 +/- 56.6*</td>
</tr>
<tr>
<td>Mean systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmHg)</td>
<td>176 +/- 24</td>
<td>157.2 +/- 21.3</td>
<td>163.9 +/- 21.7</td>
</tr>
<tr>
<td>Mean diastolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmHg)</td>
<td>130 +/- 50</td>
<td>108.3 +/- 20.6</td>
<td>115.4 +/- 20.8</td>
</tr>
<tr>
<td>Mean serum creatinine (mg/dL)</td>
<td>0.87 +/- 0.19</td>
<td>0.86 +/- 0.21</td>
<td>0.86 +/- 0.50</td>
</tr>
<tr>
<td>Mean plasma renin activity (ng/ml/hr)</td>
<td>9.64 +/- 5.7</td>
<td>6.65 +/- 6.7</td>
<td>7.6 +/- 6.4</td>
</tr>
<tr>
<td>Peripheral vein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right renal vein</td>
<td>13.42 +/- 2.05</td>
<td>7.16 +/- 7.28</td>
<td>11.61 +/- 7.77</td>
</tr>
<tr>
<td>Left renal vein</td>
<td>11.09 +/- 4.06</td>
<td>7.01 +/- 4.75</td>
<td>8.6 +/- 7.56</td>
</tr>
<tr>
<td>Positive Captopril test (%)</td>
<td>76%</td>
<td>95%</td>
<td>89%</td>
</tr>
<tr>
<td>Positive Captopril Scintigraphy (%)</td>
<td>69.2</td>
<td>95%</td>
<td>86%</td>
</tr>
<tr>
<td>Renal artery stenosis (&gt;60% lumen reduction)</td>
<td>16 (100%)</td>
<td>16 (100%)</td>
<td>16 (100%)</td>
</tr>
</tbody>
</table>

*p<0.05

(24.5%) and 5 bilateral (11.1%), four cases of longitudinal narrowing renal artery (8.9%) without a specific stenosis with a reduced kidney size (atrophic or hypoplasia), one case (2.2%) with renal angioma, one arteriography (2.2%) which was not useful in defining artery disease for technical reasons, and in 23 patients (51.1%), the study was normal. Extra renal lesions (aorta, mesenteric or cerebral) were not found, although no systematic study was done for this purpose.
in the five years of follow-up. In two children, PTA was combined with surgery, one boy (age 14 with bilateral stenosis), underwent an autotransplant and one girl (age 15 with an unilateral stenosis), underwent a nephrectomy after total renal artery obstruction one year after PTA. A nephrectomy of a small atrophic dysfunctional kidney with main artery stenosis and unilateral plasma renin production was performed in five children (median age 12.5 years old) and a hiltum pheochromocytoma resection in a patient with direct arterial compression. The results of long-term follow-up for those children treated with surgical procedures were excellent, hypertension was cured and kidney function was preserved in all cases. Mean serum creatinine levels were within normal limits during all follow-up periods.

Discussion

The underlying causes of significant hypertension in the pediatric population differ considerably from those of adults. While the prevalence of hypertension in children is lower than adults, secondary hypertension is more frequent, with children accounting for 75%-80% of cases. The most frequent causes during adolescence and childhood include renal parenchyma diseases and renal artery stenosis as major causes of elevated diastolic pressure. In the last 15 years of a screening program for RVH detection in a selected group of hypertensive children with one or more clinical suspicious signs, 16 patients (35.6%) were diagnosed as having RVH. Renovascular hypertensive patients were younger than non-RVH patients, but without statistical significance (mean age 13.94 ± 3.92/15.04 ± 3.72 years old), although gender and race distribution was similar in both groups. The mean BP in our patients was moderate/severely elevated, especially mean diastolic blood pressure (p<0.012) in RVH cases in which two patients presented hypertensive encephalopathy as the first sign of their arterial hypertensive disease. In general, only a small percentage of patients were symptomatic at the beginning of the study, as has been reported elsewhere.

The majority of the children had elevated plasma renin activity, especially in RVH patients, but no statistical significance level between RVH and non-RVH patients was found. Renal vein renin ratio levels were not useful in our series in predicting a positive response to revascularization since the number of tests was too small or failed to demonstrate lateralization in the presence of hemodynamically significant renal artery stenosis for several reasons (errors in technique, dilution of renal blood, bilateral stenosis, vascular damage secondary to hypertension, etc).

The utility of non-invasive imaging tests has not been well studied in children, although some established guidelines for the application of this test are available. In experienced centers, the combination of different tests shows adequate correlations with renal arteriography and provides evidence for therapy procedures results. In our series, the captopril-stimulated plasma renin test (positive response 76% in RVH and 52% in non-RVH patients, p<0.05), and captopril scintigraphy, correlated with arteriography (positive test 69.2% in RVH and 23.5% in non-RVH patients, p<0.01), both with statistical significance levels; showed a sensitivity (75% and 76.9%), specificity (52.9% and 76.4%); and predicted value for the presence of renal artery stenosis (96.5% and 76.6%) respectively. In experienced centers, the combination of both tests shows a high sensitivity and specificity in identifying patients with clinical suspicion of RVH, evaluating the efficacy of revascularization procedures, and in providing a BP prediction response to PTA or surgery.

This series, albeit small, suggests that both tests could be useful for therapeutic decision and prognosis, although it could be explained by small, intra-renal artery pathology not found in our cases where selective renal arteriography pre- and post-revascularization was performed. Other imaging tests like spiral CT angiography (CTA) and magnetic resonance angiography (MRA), can be useful for diagnostic purposes in selected cases, but should not be used for screening purposes in patients with moderate clinical suspicions of RVH due to cost/affecivity, large radiation exposure, and the large quantities of contrast medium in CTA and MRA, which only recognize main artery abnormalities. These non-invasive diagnostic procedures correlate strongly with arteriography. Both technologies were not available for many years in our service. Additional investigative techniques such as Doppler ultrasonography, is mainly utilized in adults and there is limited data in children. Renal arteriography remains the gold standard radiological test in the diagnosis and treatment of RVH. This study gives us the exact location of the disease, helps in determining the etiology in most cases and also gives us adequate information in reference to the extension of the arterial lesion.

The most common cause of RVH disease in children is fibromuscular dysplasia. The most frequent etiology of RVH in our series was fibromuscular dysplasia, accounting for 68.7% of patients – a figure similar to one reported in Broekhuizen-de Gast et al.,[6] and in higher prevalence than that seen in the study by Estepa R. et al.[5], McTaggart SJ et al.[7] and Chalmers RT et al.[10] The aims of the treatment modalities, medical treatment, PTA and surgery, were the control of arterial blood pressure and the preservation of renal function. The loss of renal function in RVH can be secondary to either a complication of invasive manipulation of the renal artery, or as a consequence of a progressive narrowing of the native renal artery. Adequate diagnosis is especially critical in children where the stenosis is often bilateral; this was found in 11% of our patients (31% of RVH patients). A significant stenosis carries the risk of long-term loss of renal mass function, although these changes can occur with fibromuscular dysplasia as well. However, total occlusion and renal failure are rare events in children. On the other hand, a very important factor

Table 2: Blood Pressure Control With Various Treatment Modalities in 45 Hypertensive Children

<table>
<thead>
<tr>
<th></th>
<th>Surgery n = 10</th>
<th>PTA n = 28</th>
<th>Drug treatment n = 28</th>
<th>Total n = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive without drugs</td>
<td>7 (100%)</td>
<td>7 (70%)</td>
<td></td>
<td>14 (31.1%)</td>
</tr>
<tr>
<td>Normotensive with antihypertensive drugs</td>
<td>-</td>
<td>3 (30%)</td>
<td>26 (92.9%)</td>
<td>29 (64.5%)</td>
</tr>
<tr>
<td>Lost during follow-up</td>
<td>-</td>
<td>-</td>
<td>2 (7.1%)</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>7 (15.6%)</td>
<td>10 (22.2%)</td>
<td>28 (62.2%)</td>
<td>45 (100%)</td>
</tr>
</tbody>
</table>
to take into consideration is that the rate of progression after operative intervention can be delayed in some patients. The rate of renal artery restenosis after PTA has been reported to be higher in some cases than in patients who have had their diseased vessel left intact. These observations are thought to be due to an accelerated thrombosis and/or neointimal formation resulting from post-PTA vascular injury.[7,10,16] This is one reason why in children, any invasive non-surgical intervention is controversial. However, most children benefit from these interventional procedures.[7,10,20]

In our series, PTA was indicated in ten patients (in two children, PTA was combined with surgery, one boy underwent an autotransplant and one girl underwent a nephrectomy after renal obstruction one year after PTA) with median age 14.8 years. All PTA patients remain normotensive, seven without drugs and three with drugs, albeit in a small dosage. Surgical management was indicated in seven patients, four nephrectomy of a small atrophic, with main renal artery stenosis and dysfunctional kidney, one nephrectomy in a non-RVH patient with longitudinal narrowing renal artery (with a atrophic kidney with unilateral plasma renin production), one hilum pheochromocytoma resection and one polar nephrectomy for an angioma in a non-artery stenotic-RVH patient. Hypertension was cured in all surgical cases. Comparing therapeutic results, those of our patients who underwent surgery had better outcomes than those treated by PTA, but our number of patients is too small to bring statistical results.

We conclude that it’s possible to find a high prevalence of RVH in any population of hypertensive children with suspicious clinical signs and that renal arteriography must be included in their work-up in order to make a proper and timely diagnosis and treatment. Non-invasive tests such as captopril-stimulated plasma rennin and captopril scintigraphy are useful for diagnosis and therapeutic decisions, although renal angiography remains the gold standard radiological procedure for accurate evaluation, diagnosis and treatment. PTA, surgery or a combination of PTA and surgery in patients with RVH, controls arterial blood pressure in the majority of patients and subsequently preserves their renal function.

REFERENCES


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CUBAN MEDICAL LITERATURE

Broad Use of Cuban Recombinant Human Erythropoietin (ior-EPOCIM) in Dialysis Patients at the Institute of Nephrology

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AM Lagarde, MD(2);
R Herrera Valdés, MD, PhD(1);
AI Martínez, MD(1);
ME Raola, MD(1);
Ch Magrans, MD, PhD(1)

ABSTRACT:
The results obtained using Cuban human recombinant alpha erythropoietin, ior-EPOCIM, at the Institute of Nephrology, Havana, are presented. From June 1999 to June 2001, 143 hemodialysis patients with renal anemia were treated during a minimum of four months with initial subcutaneous 30 U/Kg dosage. Results: 88% of the patients met criteria for satisfactory response, hematocrit rising from 22.1% to 33.1%. The average weekly dosage of EPOCIM, individually adjusted to maintain a target hematocrit of no less than 33%, ranged from 87 to 105 U/Kg. The number of transfused patients was reduced from 94.4% before treatment to less than 24.5% at the end of the study. The only complication detected was transient arterial pressure increase, not associated with other complications and not requiring interruption of r-HuEPO use. In short, ior-EPOCIM showed results similar to other international commercial r-HuEPO for improving and correcting renal anemia. As a result of this research, progressive national extension of the product was begun, free of charge to all patients in hemodialysis.

Keywords: RENAL ANEMIA, ERYTHROPOIETIN, HEMODIALYSIS

INTRODUCTION

The progressive damage caused by chronic renal failure (CRF) leads to insufficient production of erythropoietin (EPO), in turn resulting in anemia. EPO is a glycoprotein secreted in the kidney in response to hypoxia, and is the main regulator of erythrocyte production. This regulation occurs by stimulation of red bone marrow cells through membrane receptors on the erythroid colony forming cells, which proliferate and differentiate, thus increasing hemoglobin levels.[1] For this reason, anemia is common in these patients, although multiple other factors may contribute to it, such as the shortening of the erythrocyte half life, lack of iron, folates and/or vitamin B12, hemoglobinopathies, etc.

During the hemodialysis stage, other mechanisms may worsen it: repeated blood loss, absolute and functional iron shortage, malnutrition, hemolysis, aluminum toxicity, bone marrow fibrosis, infections, and a chronic inflammatory state caused by the continuous exposure of blood to extra-corporeal circuits.[2,3] Physiopathologically, chronic tissue hypoxia is the most important uremic toxin, demonstrated by the different systemic changes it causes, directly affecting morbidity and mortality rates and rehabilitation of these patients.[4]

Severe anemia was controlled by blood transfusions with all its associated risks: biological, because of the potential transmission of infectious agents; allergic and immune, producing incompatibility and sensitization to histocompatibility antigens, thereby reducing opportunities for successful kidney transplant; and clinical, due to volume overload, risk of hyperpotassemia, iron overload, etc.[5] Human recombinant EPO (r-HuEPO) emerged as a solution for kidney anemia in 1986. Its cardiovascular and non-cardiovascular efficacy and benefits, and the improvement of patients’ general well-being, allow us to state that its advent marks the beginning of a new era because of the change in quality of life for dialysis and transplant patients.[6,7]

Only a few companies have patented this drug, raising the already high price of substitution therapy with similar clinical efficacy.[8] The production of erythropoietin in Cuba by CIMAB using recombinant DNA techniques and its registry based on a clinical trial carried out by our center and CIMEQ (the Spanish acronym for its name: Medical-Surgical Research Center),[9] enabled use of this hormone for all hemodialysis patients at the Institute.

The objective of this study was to analyze improvement or correction of anemia in our patients, using ior-EPOCIM.

MATERIAL AND METHODS

An open, clinical prospective study was carried out with nationally produced human alpha r-HuEPO (ior-EPOCIM) in 143 adult patients with ESRD. All were being treated by hemodialysis with < 28% hematocrit levels, had not used erythropoietin previously, and had completed four months of treatment starting in June 1999. The 143 patients studied until June 2001 averaged 42.8 years old and had received hemodialysis treatment for an average of 61.2 months. They all received erythropoietin treatment subcutaneously at an initial dosage of 30 U/kg/dose three times a week. The dosage was increased according to response, or reduced if the hematocrit was > 36%. Iron Dextran was administered endovenously during the first 10 weeks at 100 mg/week and at 50 mg/week thereafter, as a maintenance dosage.

Samples for analysis were collected mid-week, on an empty stomach, by puncture of the arteriovenous fistula. Hematocrit determinations were carried out at the hematological complex COBAS-ARGOS 5 DIFF, Roche, France. Hematocrit
increase in % with respect to the individual basal level was taken into account to establish efficacy. Increased hematocrit e 6% over the basal level without blood transfusion, was considered a satisfactory response. Linear regression was calculated for hematocrit variations with respect to treatment duration variance analysis, with a significance level of 0.05.

RESULTS

A satisfactory response was observed in 126 patients after four months of treatment (88%).

Statistically significant increase in hematocrit rose from 22.4% before treatment with ior-EPOCIM, to 33.1% using individually adjusted dosages.

Hematocrit values over 30% were observed in 69% of patients. Only 11 patients (7.69%), showed hematocrit values higher than 28%, but all had increased more than 3% over the basal hematocrit.

The number of transfused patients fell from 94% before the treatment to 24.5% after four months, which was characteristic for this dosage-adjustment phase and conditioned by individual response to r-HuEPO and the appearance of complications typical of ESRD.

The only adverse effect found was the appearance or worsening of high blood pressure (HBP) in 53% of total cases, reaching a maximum of 63% of patients by the second month of treatment in 63% of the patients, and dropping to 34% by the fourth month.

HBP was not associated with serious secondary complications, nor was it necessary to interrupt use of ior-EPOCIM.

DISCUSSION

Reports indicate that up to 80% of patients at the beginning of hemodialysis have anemia. In our work, we found that practically all our patients had anemia, which indicated a delayed inclusion in dialysis.

The target hematocrit with r-HuEPO treatment has changed over time. Initially the 1998 DOQI guidelines placed it between 30-33%, later increased to 33-36%. This value is similar to the target of the European Best Practice Guidelines, which point out that less than 50% of patients do not reach that goal. We aimed at having our patients reach a hematocrit of no less than 30%, result attained by 69.22%. Hematocrits higher than 33% were found in 47.55% of patients.

It has been demonstrated that to achieve the planned hematocrit level in the initial phase of dosage adjustment, the time required for anemia correction fluctuates between one and four months. The various increases in hematocrit levels during the period under study, and with the EPOCIM dosages used, are in accordance with those described in other clinical trials.

It has been reported that 23% to 77% of patients do not reach the proposed hematocrit level until after three months of treatment. Only 10% of patients require dosages higher than 300 U/Kg/week subcutaneously to attain this. Average dosages in Europe vary from 93 to 161 IU/Kg/week. The dosage required in this study to reach the proposed hematocrit values were within this range.

There is the opinion that the target hematocrit is easier to attain with peritoneal dialysis than with hemodialysis, and that higher r-HuEPO dosages are necessary in the latter procedure. All our patients received ior-EPOCIM subcutaneously at an average maximum dosage of 107.4 U/Kg/week.

Table 1: Response to Cuban r-HuEPO (ior-EPOCIM) Treatment

<table>
<thead>
<tr>
<th>Patients in Follow-up (n=143)</th>
<th>Months in Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Ht. (V %)</td>
<td>23.9</td>
</tr>
<tr>
<td>Dosage EPOCIM (U/Kg/Week)</td>
<td>94.2</td>
</tr>
<tr>
<td>Satisfactory Response (%)</td>
<td>10</td>
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</tbody>
</table>

Note: Hematocrit prior to ior-EPOCIM treatment: 22.4 V%. *p< 0.05 **p< 0.001

Figure 1: Hematocrit Response and Percent of Patients Transfused during ior-EPOCIM Use

Source: Department of Hemodialysis, Institute of Nephrology. 2002.
The main adverse event directly related to r-HuEPO is high blood pressure, which must be controlled prior to beginning treatment and closely monitored thereafter. An increased dosage of antihypertensive agents may be required, or HBP may reappear in a controlled patient. Such an increase is usually temporary, but must be monitored to avoid typical complications of severe HBP.

Clinical factors that predict risk of HBP development are: its presence in the predialytic stage; degree of anemia; rate of hematocrit increase; maximum hematocrit reached; r-HuEPO dosage; and endovenous application. Several mechanisms explain HBP in these patients: hematocrit increase leading to a rise in blood viscosity and elimination of hypoxic vasodilatation; activation of the sympathetic system of renin-angiotensin; lack of balance in the synthesis of vasactive substances in detriment to vasodilating ones; inactivation of the nitric oxide system; direct vascular action caused by intracellular calcium increase in the smooth vascular muscle; vascular receptor stimulation; and rise in vascular reactivity to endotelin I and angiotensin II.

In conclusion, this experience with ior-EPOCIM confirms its prompt extension to all patients in the country will be just successful.

**Table 2:** Percent of Patients with Changed Hematocrit by 4th Month of Treatment

<table>
<thead>
<tr>
<th>Hematocrit (V %)</th>
<th>Number of Patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 26</td>
<td>21</td>
<td>14.68</td>
</tr>
<tr>
<td>26 to 29</td>
<td>23</td>
<td>16.08</td>
</tr>
<tr>
<td>30 to 33</td>
<td>31</td>
<td>21.67</td>
</tr>
<tr>
<td>33 to 36</td>
<td>54</td>
<td>37.76</td>
</tr>
<tr>
<td>36 or more</td>
<td>14</td>
<td>9.79</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>143</td>
<td>100</td>
</tr>
</tbody>
</table>

*Source: Department of Hemodialysis, Institute of Nephrology. 2002.*

When analyzing this phenomenon, it becomes clear that it is ESRD that determines HBP appearance, since use of r-HuEPO in chemotherapy and anticancer drug-induced anemia in newborns, AIDS and multiple myeloma patients, is not associated with a rise in blood pressure, despite endovenous administration and use of dosages up to five times higher.

In our patients, HPB was carefully managed, evaluating whether hematocrit values were related to it and adjusting the pharmacological treatment accordingly. Changes were made in dialysis indication (adjustment of dry weight, change of dialysis machines, and increase in the length of hemodialysis). In our experience, HPB events were transitory and could be corrected, and they were not associated with severe secondary complications, or the need to interrupt ior-EPOCIM treatment.

In any case, a risk-benefit analysis shows cardiovascular advantages and benefits are much greater than the temporary appearance of HBP.

In conclusion, this experience with ior-EPOCIM confirms the efficacy of Cuban r-HuEPO and its safety, predicting that its prompt extension to all patients in the country will be just as successful.

**Table 3:** High Blood Pressure Behavior with Cuban r-HuEPO (ior-EPOCIM) Treatment

<table>
<thead>
<tr>
<th>Months of Follow-up</th>
<th>Patients in Follow-up (n=143)</th>
<th>HBP %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beginning of Hemodialysis</td>
<td>1</td>
</tr>
<tr>
<td>HBP (%)</td>
<td>33.56</td>
<td>37.06</td>
</tr>
</tbody>
</table>

*Source: Department of Hemodialysis, Institute of Nephrology. 2002.*

(To date, April 2005, all patients undergoing dialysis and transplant patients with graft malfunctions, are receiving ior-EPOCIM free of charge. *The Authors*.)

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CUBAN MEDICAL LITERATURE

Use of Recombinant Streptokinase for Hemodialysis Catheter Recovery

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ABSTRACT

Patients with end-stage renal disease in dialysis survive thanks to tri-weekly purification of their blood supply, requiring access to blood circulation by an arteriovenous fistula, surgically created months before its use, or by central venous catheter. Malfunction of the latter can cause catheter loss and treatment interruption, requiring catheter replacement, which is not without complications. Since October 2001, 20 intraluminal Heberkinasa infusion procedures were performed in the 15 patients with such malfunction, resulting in 85% catheter recuperation, with only three catheters lost. There was good tolerance of the product, with 20% minor and temporary associated events. This study demonstrates that Heberkinasa administered in this way is safe and efficacious, which makes it a reasonable alternative for this frequent problem. It prevents final catheter loss and has positive effects on social and human cost effectiveness by avoiding potential risks of multiple catheterisms. The validity of these results has led to generalizing such practice in hemodialysis centers throughout Cuba.

Keywords: ANTICOAGULATION, CATHETER DYSFUNCTION, HEMODIALYSIS.

INTRODUCTION

End-stage renal disease (ESRD) is the end road for diseases such as diabetes mellitus, high blood pressure (HBP), glomerulopathies and others associated with the aging of the world population, developing progressively towards the terminal stage, requiring dialysis or transplantation.

Hemodialysis patients survive thanks to the cleansing of their blood tri-weekly, requiring surgically created access to their blood supply, or without this, a central venous catheter. The latter represent about 15% to 25% of the total number of hemodialysis patients. Malfunction of the catheter is an important complication that causes a reduction in blood flow, interruption of hemodialysis, and loss of the catheter, necessitating replacement, which is not free from complications and leads to more risks of complications and potential mortality.[1]

This is a frequent problem and is responsible for the loss of over 1/3 of the catheters in the initial stages of their placement.[2]

To avoid catheter malfunction caused by fibrin or thrombosis, pure heparin is instilled into each branch of the catheter according to its volume, and removed prior to beginning treatment. If the amount instilled is greater than needed, the risk of anaphylactic or immunologic systemic effects increases. If the amount is less than required, it increases the risk of intra-catheter coagulation, or just as, if not more important but less studied, it may lead to peri-catheter thrombosis. This thrombosis formation contributes to catheter malfunction, formation of central vein stenosis, the appearance of embolisms and significant septic complications if it becomes infected.[3]

As an alternative to heparin instillation, which is used as an anticoagulant after every hemodialysis, other more expensive agents such as recombinant urokinase and rtPA (recombinant tissue-plasminogen activator), have been used without
superior results. Faced with catheter malfunction or coagulation, several thrombolytic protocols have been used, with none appearing to offer the definitive solution to this commonly found problem in hemodialysis.[4,5]

The use of high cost, permanent tunnel catheters as the only final alternative for patients when there is no possibility of performing an arteriovenous fistula or prosthetic graft, illustrates the need for a more urgent approach and solution to this situation. These factors prompted the study described here.

PATIENTS AND METHODS

A prospective study was carried out at the Institute of Nephrology, using Cuban human recombinant streptokinase (Heberkinasa, Center for Genetic Engineering and Biotechnology, HeberBiotec S.A.), if there was no contraindication for its use, in 15 patients who presented severe catheter malfunction from October 2001 to April 2002.

Heberkinasa is used widely in Cuba for acute myocardial infarction and was used in nephrology for the treatment of arteriovenous fistula thrombosis from 1994-1996.

Blood flow and venous and arterial pressures are routinely monitored to alert for potential access problems during every hemodialysis. At the end of treatment, the lumen of each branch of the catheter is filled with pure heparin, in liquid volume amounts established by the manufacturer.

The warning sign for a poorly functioning catheter was established as a reduction of blood flow to less than 200 ml/min.

Figure 1: Algorithm for Use of Recombinant Streptokinase

Definitions:
Severe catheter malfunction: failure to carry out hemodialysis procedure due to coagulation in catheter lines or low flow preventing its performance.

Saved catheter: if the catheter remained in place three months after the event or was removed for reasons unrelated to recurrent clotting.

Loss of the catheter: if it became necessary to replace the catheter due to malfunction.

Application Protocol

Faced with the impossibility of performing hemodialysis, nursing staff halted the process and sought physician corroboration, after which the physician temporarily hospitalized the patient. The physician then instilled 375,000 IU of Heberkinasa into each catheter branch (intraluminally), with continuous cardiovascular monitoring for three hours. Afterwards, Heberkinasa was removed by aspiration, the branches washed and heparin left in them to restart hemodialysis. The dosage of anticoagulant used was specific to each case. If the malfunction persisted, the procedure was repeated. If it was effective, but was recurrent in the following hemodialysis, the procedure was carried out again, but limited to a maximum of three instillations.

The procedure was used for eight patients with permanent catheters and seven with transitory, the latter used for the development period of the arteriovenous fistula catheters.

Descriptive statistics were used for analyzing the results.

RESULTS

Of the 20 intraluminal Heberkinasa instillations administered to 15 patients with catheter malfunction, repetition of instillation was required in two patients and two more patients required three administrations, for 25% of the total instillations.

Three months after instillation, in 17 out of 20 applications (85%), there was vascular access using the saved catheter, eight of which were temporary and seven permanent, and only three of the 15 patients needed a catheter change (one catheter was permanent and two temporary).

Catheter loss occurred in 15% of the procedures, one loss occurred 67 days after the first administration (permanent catheter); the other two occurred in patients with temporary catheters. Of these, in one patient the loss occurred following two more instillations, after six and 28 days respectively. The other patient was also instilled three times (the first interrupted due to precordialgia without changes in cardiac monitoring, followed by a precarious hemodialysis, and reinfusion on the next day with catheter permanence of 35 days and a last attempt with a permanence of only five days).

The adverse events using this product were all temporary and minor. They were found in 20% of patients and consisted of sinus tachycardia (3), extrasystolic sinus arrhythmia (2), lumbar and thoracic pain (1), nausea (1), and mild increase of arterial pressure (1). It was necessary to stop the procedure in only one patient, removing the drug because of thoracic and lumbar pain without any change in cardiovascular monitoring. The procedure was repeated hours later with-
out any modifications. More than one event was observed in four of the affected patients.

DISCUSSION

Techniques of vascular access to circulation are essential for carrying out hemodialysis and whether temporary or permanent (arteriovenous fistula, vascular graft or tunnel catheter), they are still the Achilles’ heel in guaranteeing the quality and efficiency of the purification session, despite advances achieved in recent years.[3]

If it is necessary to use a catheter as an alternative to the arteriovenous fistula, this also presents potential medical complications at the time of insertion. Other complications may appear in short or long term management such as: infection at the site of entry or of the tunnel; colonization (possibly causing a chronic micro- or systemic inflammatory state); central vein stenosis depending on the one-time or repeated placement of the catheter through the subclavian or even jugular vein; and poor flow, which may be due to twisting of the catheter or the obstruction of the blood entry/exit openings due to fibrin or clotting within or around the catheter leading to its malfunction.[1,4]

Catheter thrombosis is considered the most important cause of malfunction, and the resulting adverse effects should not be assessed only in terms of the high cost of the catheters themselves and loss of continuity and efficacy of the dialysis session, but also in terms of the potential risks of subjecting the patient to multiple traumatic interventions, with the negative implications of attendant stress, and the effect on mortality.[4]

This study describes our experience using a recombinant streptokinase infusion protocol. Streptokinase was instilled in the lumen of each hemodialysis catheter line for three hours, after which it was removed.

The instillation frequency used was in the same range as that of other reports using different thrombolytic agents.[6,7]

Our frequency of catheter change was similar to the one reported by Welik et al. also using recombinant streptokinase,[2] but we reported slightly inferior results than those for other more modern anticoagulants. Nevertheless, we must take into account that the time factor is essential when considering efficacy, since different authors using different thrombolytic agents and/or different protocols report efficacy in different ways, even the possibility of carrying out hemodialysis immediately with tPA in 87.5%.[8]

Takeda[5] used urokinase with an 84% catheter survival after 34 days, which is similar to our results. Webb[9] using a systemic urokinase infusion followed by permanent oral anticoagulants, reported 95% recovery after three months.[9]

The most commonly used drugs for catheter malfunction, in the order they appeared are increasingly more expensive: streptokinase, urokinase and recombinant tissue plasminogen activator (tPA).[10]

Clase points out the safety, efficacy (streptokinase 70%; urokinase 80%; tPA 83-98%), and increasing costs of each.[11]

We did not find important adverse effects, even when the procedure was interrupted for thoracic and lumbar pain and repeated some hours later in one patient. All this is caused by the passage of small amounts of recombinant streptokinase through a catheter opening. We did not find allergic reactions or severe effects related to its use as reported by others.[11]

Analyzing the cost of recombinant streptokinase when compared to the catheter, and considering the efficacy achieved, our results show a positive cost-benefit balance. Even more so if we consider that Heberkinasa is produced in Cuba; the use of other thrombolytic agents is prohibitive because of their very high prices in the international market.[10,11]

In short, this study, in which a protocol of simple Heberkinasa intraluminal instillation is used for hemodialysis catheter malfunction, showed that it is safe, well-tolerated and efficacious. This makes it a reasonable, cost-effective alternative, in our circumstances, for solving this important and frustrating problem. It also avoids definitive catheter loss, and thus has a positive impact on cost-effectivity and patient care, reducing complications and mortality caused by repeated venous interventions, which also lead to irreversible vessel loss.

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THE AUTHORS

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MEDICAL LITERATURE - ABSTRACTS

Relationship Between Weight at Birth and the Number and Size of Renal Glomeruli in Humans: A Histomorphometric Study

Reynaldo Mañalich, Leonardo Reyes, Mercedes Herrera, Clara Melendi, Isabel Fundora

Background. The number of nephrons in humans varies considerably under normal circumstances, and retarded intrauterine growth has been reported to be associated with a significant reduction in nephron number. Low nephron number may be an independent risk factor for the development of hypertension. We therefore decided to evaluate the relationship between body weight at birth and the number and size of nephron units.

Methods. We examined coronal sections of the kidneys of 35 neonates who died within two weeks of birth because of hyaline membrane, infectious complications, brain hemorrhage, or perinatal hypoxia and had no urinary congenital malformations. Nine of them (5 males and 4 females) were between 36 and 37 weeks of gestation, and the rest had 38 or more weeks of gestation. Eighteen neonates weighed less than 2500 g at birth (low birth weight; LBW; 9 females and 9 males), and 17 had weights above this value (normal birth weight; NBW; 8 females and 9 males). In each section, glomeruli present in four sequential subcapsular microscopic fields, corresponding to 0.6 mm², were counted; in addition, the area of each of 65 consecutive glomeruli was determined by a computerized measurement system. Glomerular volume was calculated from the glomerular area. Linear regression analysis was used to test the relationship between glomerular number and size and the weight at birth.

Results. The number of glomeruli per 0.6 mm² of renal cortex was 92.9 ± 4.85 in the LBW and 105.8 ± 3.91 in NBW (P < 0.0001). Glomerular volume (µm³ ÷ 10⁻³) was 529.1 ± 187.63 in the LBW group and 158.0 ± 49.89 in the NBW group (P < 0.0001). The glomeruli occupied 8.59 ± 1.38% of the kidney area under examination in the LBW group and 14.3 ± 2.75% in the NBW group (P < 0.0001). There were significant direct correlations between the weight at birth and the number of glomeruli (r = 0.870, P < 0.0001) and area occupied by glomeruli (r = 0.935, P < 0.0001). There were inverse correlations between the number of glomeruli and the volume of the glomeruli (r = -0.816, P < 0.0001) and the weight at birth and glomerular volume (r = 0.848, P < 0.0001). These findings were independent of sex and race (black vs. white). Essential arterial hypertension existed in 38.9% of the mothers of children with LBW and in 5.9% of the mothers of children with NBW (P < 0.05). Smoking habits existed in 50% of the mothers of LBW children and in 11.8% of the mothers of NBW children (P < 0.05).

Conclusion. There are strong correlations between glomerular number (direct) and size (inverse) with LBW in this cohort. Endowment with decreased nephron numbers may be a risk factor for hypertension and the rate of progression of renal disease.

Keywords: LOW BIRTHWEIGHT; ARTERIAL HYPERTENSION; SMOKING; PROGRESSIVE RENAL DISEASE; INTRAUTERINE GROWTH


Demographic and Epidemiologic Transition in the Developing World: Role of Albuminuria in the Early Diagnosis and Prevention of Renal and Cardiovascular Disease

Ricardo Correa-Rotter, Sarala Naicker, Ivor J. Katz, Sanjay K. Agarwal, Raúl Herrera Valdés, Dan Kaseje, Bernardo Rodríguez-Iturbe, Faissal Shaheen, Chitr Sitthi-Amorn

The developing world is facing a real pandemic of renal and cardiovascular disease. With the decrease of infectious disease morbidity and mortality, and the exposure to a more westernized lifestyle, signs of increasing renal and cardiovascular disease is particularly shown in the tremendous rise in type 2 diabetes and its sequelae. A group of doctors and scientists from all over the world have convened in Bellagio to halt this dramatic disease change and burden to developing countries. They came to the conclusion that screening and treatment should clearly focus on cost-beneficial strategies, among which blood pressure and urinary albumin measurement, as well as effective and affordable treatment strategies to lower blood pressure and albuminuria, are essential.

Keywords: MICROALBUMINURIA; KIDNEY DISEASE; DIABETES MELLITUS; ÉPIDÉMIC; DEVELOPING WORLD; TYPE 2 DIABETES


TOP STORY

Cuba Marks 15 Years
Treating Chernobyl Victims

By Conner Gorry

When disaster strikes, the world is riveted. Who can forget Mt. St Helen’s spewing ash over Washington State or the thousands of corpses stacked like logs after the chemical plant catastrophe in Bhopal, India? Unfortunately, once the immediate crisis is contained and the headlines shift to the next big story, world attention fades. This is precisely what happened after the nuclear accident in Chernobyl, now largely forgotten in many places. But not in Cuba, where over 18,000 children and young adults have been treated for a panoply of illnesses over the past 15 years.

Ukrainian Health Minister Nykola Efremovish Polischuk was in Cuba recently to commemorate the anniversary. In remarks delivered at a ceremony in Havana’s Teatro Nacional, he pointed out that the island nation is one of the few countries to have extended aid to Chernobyl’s victims. The ongoing and sustainable medical nature of this aid is what distinguishes the Cuban program and has led to broadened bilateral relations over the past 15 years.

The Explosion

On April 26, 1986, the central reactor at the nuclear plant in Chernobyl, Ukraine exploded and caught fire, killing dozens and inciting panic as plumes of radioactive smoke spread outward; the toxic fallout eventually killed thousands. Children were among the first to be evacuated in a massive exodus that saw 150,000 people abandoning their homes and workplaces; everything for a 30-km radius from the reactor was left behind in the evacuation, creating an instant ghost town.

Aid was swiftly dispatched in the disaster’s aftermath and many orphaned children found safety with adoptive parents in Spain, Italy, France and Germany; recreational programs and group vacations for affected children were also offered by various countries including Italy, Israel and Spain. But after a few years, the disastrous event in Chernobyl was eclipsed by other catastrophes, even though thousands were still - or becoming - sick.

Cuba Offers Medical Treatment

Mounting evidence about the nature and scope of the radioactive fallout led the Cuban government to establish its “Chernobyl Children” program at the Tarará Pediatric Hospital in 1990. The idea was to provide free, comprehensive medical care to the most severely affected children aged 5-15 years from the region. From the first group of 139 severely ill children who arrived in Cuba on March 29, 1990 to the nearly 800 patients - both children and adults - treated in 2004, that idea has blossomed into a concrete reality helping people of many nations get well in the wake of disasters.

The majority of the first young patients arriving from Chernobyl suffered from gastrointestinal, immunological and hematological illnesses. Endocrine problems, particularly thyroid cancer and hyperplasia, were the most common. In the earliest stages of the Tarará project, Cuban doctors and specialists treated 289 patients with leukemia and performed six bone marrow and two kidney transplants. Ukrainian officials estimate the Cuban government
has spent some US$300 million to treat these thousands of children – far and away more than any other country has offered the victims of Chernobyl.

In an exclusive interview with MEDICC Review, Dr. Julio Medina, Director of the Tarará Pediatric Hospital said “the first cases we saw had thyroid-related illnesses – these were the first effects of the accident. Today, we consider posttraumatic stress disorder the second effect of the accident.” Genetic malformations - especially in the kidneys - resulting from radioactive exposure, and skin disorders like vitiligo, are other long-term effects being treated at Tarará.

Like all patients in the Cuban public health system, the Chernobyl kids are treated using an integrative approach that includes a wide array of specialists - from pediatricians and oncologists, to psychologists and dentists. They also benefit from the latest advances in Cuban biotechnology, receiving hepatitis B and other vaccinations and recombinant interferon therapy.

Dr. Medina added that though officials “peg the number of victims at 100,000, it is very difficult to say...because the area is still contaminated.” Since much of that contamination is with Cesium 137, (with a half life of between 20 and 50 years), coupled with the fact that some evacuees are repopulating Chernobyl after 19 years away from home, it’s likely the doctors at Tarará will continue to treat a fair number of comely children, their flaxen hair gone due to alopecia.

From Disaster to Development

Cooperation between the governments of Cuba and the Ukraine during the 15 years of the Chernobyl Children’s program has fostered a unique relationship between the two public health systems. In 1998, the governments signed an accord that brought the integrative Tarará treatment model to the Ukraine, with a Cuban medical team including an endocrinologist, pediatrician, hematologist and psychologist, arriving in the Crimea.

The working partnership on the Chernobyl project could serve as a model for other countries. In 2003, the Ukrainian Parliament took the Chernobyl Children project under consideration and voted to make it an official government program, earmarking funds for its future development.

As for the Tarará facility, it has branched out from its roots as a hospital for the victims of Chernobyl and been transformed into an international post-disaster medical center, treating children from all over the world. Earthquake victims from Armenia, Brazilian children suffering from Cesium 137 poisoning and traumatized families evacuated from Montserrat when the volcano on that island rendered it almost entirely uninhabitable, all have benefited from the expertise and solidarity of the Tarará Pediatric Hospital.

Post-Chernobyl

- 60% of the effected population has fears about the food supply and suffers from insomnia, irritability and a feeling of helplessness
- 30% has lost any interest in life

Data from Center for Democratic Initiatives, an NGO interviewing victims ten years after the explosion.

Nineteen years later, Cuba continues to treat children from Chernobyl.
HEADLINES IN CUBAN HEALTH

Cuba Announces New Cholera Vaccine
At “Health for All” Trade Fair

Havana, April 20 - Scientists at Cuba’s Finlay Institute have announced the successful completion of clinical trials on a vaccine against cholera, after 14 years of research. The vaccine candidate was jointly developed by researchers at the institution, the Pedro Kouri Tropical Medicine Institute and the National Center for Scientific Research (CENIC). The announcement came at the 12th “Health for All” International Trade Fair in Havana this week, attended by over 330 pharmaceutical, laboratory and medical equipment companies from 29 countries in Asia, Europe and the Americas.

Between five and seven million people are victims of cholera annually, the result of contaminated water supplies. These cases, and the 120,000 deaths they provoke per year, occur almost entirely in developing countries. According to Dr. Concepción Campa, Director of the Finlay Institute, the “10/90 gap” has long been an important factor in determining Cuba’s research priorities. The gap, first described in 1990, refers to the fact that of the US$73 billion invested annually in global health research, “less than 10% is devoted to research into the health problems that account for 90% of the global disease burden (measured in Disability-Adjusted Life Years or DALYs).”[1]

One problem, says Dr. Campa, is that pharmaceutical transnationals do not see their profits linked to developing vaccines against diseases of the poor. “However, our vaccine,” she told MEDICC Review, “is not another version of the tourist vaccine against cholera that has appeared on the market. This vaccine is precisely for the poor, the main ones suffering from the disease.”

According to “The 10/90 Report on Health Research 2003-2004,” published by the Global Forum for Health Research, all but 4% of Cuba’s medical research budget is allocated to priority health topics; and Cuba is one of the few developing countries even close to the percentage of health expenditures the Report recommends be allocated for health research and capacity building.[2]

The clinical trials on the new Cuban cholera vaccine are due to be followed later this year with trials in countries where cholera is endemic, such as South Africa, Mozambique and India.

The “Health for All” Fair

Extending over six exhibition pavilions at Cuba’s “Expocuba,” the Fair (April 18-22) provided Cuban public health authorities, medical professionals and students, the opportunity to examine many of the latest advances in medical products and technologies developed in Cuba and abroad.

Cuba continues to increase its investment in medical products and technologies, making the trade fair an important commercial event for foreign companies already selling to Cuba, as well as those evaluating the Cuban market.

Among several German companies present, Schering has been selling its pharmaceuticals to Cuba for many years and participates regularly in the Fair. The Italian firm R&P Company, which began selling its ophthalmology supplies and equipment to Cuba after the last trade fair in 2003, attracted long lines of visitors eager to try its new mobile equipment for measuring vision. According to its representative, R&P hopes to convince Cuban health authorities to purchase the mobile equipment for use in rural areas and schools.

Asian firms occupied an entire pavilion, where the South Korean company Neneka, took advantage of the Fair to launch its new digital ultrasound equipment, Accudix. Several Japanese companies, including Konica Minolta, Olympus and Shimadzu, demonstrated advanced equipment for medical imaging. Shimadzu participated here four years ago and began selling its equipment to Cuba in 2002.

The Fair is also important to Cuba’s growing pharmaceutical and medical industry, showcasing the country’s growing line of products and services. The 62 Cuban entities represented included Cuban biotechnology leaders such as CIMAB, the originator of cancer vaccines and other advanced biotechnology, the Finlay Institute, producer of many innovative vaccines and antigens for vaccines, and BIOMAT, producer of materials for medical research and diagnosis.

In addition to those mentioned, the countries represented at the fair included Spain, Belgium, Switzerland, Holland, Luxembourg, Canada, Israel, India, China, Argentina, Brazil, Costa Rica, Colombia, El Salvador, Guatemala, Mexico, Panama, Peru, Venezuela, the Virgin Islands and the Dutch Antilles. Two firms from the United States also participated, Medrad and Navarreta Group-Whatham Laboratories. In addition, Ireland was represented at the fair for the first time.

References

A Decade of Medical Donations Cements Cuba-Canada Cooperation

By Conner Gorry

Ten years of any successful union – whether a marriage, business partnership or championship baseball team – doesn’t happen by chance. The task is doubly tough in the arena of international cooperation, where divergent expectations and cross-cultural differences can derail even the most well intentioned projects. Rising to the challenge is Health Partners International of Canada, (HPIC), celebrating ten years of facilitating over US$32 million worth of medical donations to Cuba.

Although HPIC has worked in over 100 countries in its 15-year history, Cuba accounts for some 25% of the organization’s worldwide donations. The Cuba project began in 1995 after then-Prime Minister Pierre Trudeau returned from a trip to the island determined to lend a humanitarian hand. Rallying the support of key government actors and officers in the Pharmaceutical Manufacturers Association of Canada, the nascent aid project sprang to life when HPIC was enlisted to administer the program and facilitate bilateral Canada-Cuba cooperation in medical materials.

In late 1995, the idea was translated into reality when US$1.8 million of medical aid arrived in Cuba. Over the ten years the two governments have worked together, HPIC has facilitated millions of dollars worth of vaccines, medicines, dialysis machines and other donations. In the wake of Hurricane Mitch in 1998, Cuba advocated redirecting the aid earmarked for the island to Central America. This act of humanitarian philanthropy was underscored by Cuba’s establishment of the Latin American Medical School, which offers full scholarships to students from underserved communities. When Cuba was throttled by its own Hurricane Michele disaster in 2001, HPIC responded with US$815,000 in donations.

More recently, HPIC facilitated the donation of 90 refurbished dialysis machines donated by St Michael’s Hospital in Toronto. Working with the International Society of Nephrology and the Canadian-Cuban Friendship Association, HPIC warehoused and shipped the machines to several hospitals in Cuba, where the donation was expected to increase dialysis capacity by 30%.

HPIC’s Cuba model has a unique design that contributes to its success. Most important, an annual list of urgently needed medicines is submitted by the Cuban Ministry of Health (MINSAP) to HPIC, which then circulates the list to Canada’s top pharmaceutical companies, including Glaxo SmithKline, AstraZeneca and sanofi pasteur, in search of donations. Placing needs assessment and prioritization in the hands of Cuban health officials guarantees that HPIC “is only shipping what [Cuba] really wants and needs,” according to Deborah Collins, HPIC’s Director of International Health Programs.

Another aspect of HPIC’s philosophy is that all medicines and equipment meet strict quality control criteria. Expiration dates are verified – nothing with an expiry date less than a year out is accepted – dosages are checked against MINSAP requirements and packaging is reviewed to ensure the medicines are viable and will arrive in tact. The goods are then shipped to Cuba with support of the Canadian International Development Agency (CIDA, the international aid arm of the Canadian government). Once in Cuba, meticulous distribution logs are kept and sent to HPIC for follow-up; over the ten-year cooperation, HPIC has performed site visits to verify that medicines were indeed received by the intended health installations in Cuba.

Underlying the logistic nuts-and-bolts of the successful cooperation is ten years of relationship building, trust and mutual respect. “It is a pleasure to work with HPIC,” says Dr Gisela Jiménez, Coordinator of Cooperation Projects for the Ministry of Health. “They are marvelous people, very serious and organized and they never put conditions on the donations. Both sides work with incredible transparency.”

“But it’s not only about donations,” avers Lise Filiatrault, Cooperation Counselor for CIDA. “It’s about sustainability.” Indeed, moving from dependency to interdependency is the priority, made evident by the HPIC delegation that visited Havana recently. Comprised of industry leaders from Canadian pharmaceutical companies, the delegates got a close look at the cutting edge of Cuban R&D, manufacturing and educational programs. There is hope that Canadian and Cuban companies can collaborate in several areas in the future, including joint research projects, exchanging best practices, and knowledge-sharing in manufacturing.

According to MINSAP’s Dr Jiménez, “the visit was very important because they saw our capacities and capabilities…I think HPIC can serve as a model for cooperation between the two countries [and] the visit opened doors for future collaborations.” Thanks to ten years of an enviable working relationship among Canada, Cuba and Health Partners International, those doors are opening to a whole new world of possibility.
Latin America’s Longest Heart Transplant Survivor, 19 Years Later

Las Tunas, Cuba—On March 29th, 34-year-old Hector Despaigne Guillen marked his 19th year with a new heart. He is Latin America’s longest surviving heart transplant patient. In 2001, Cuban surgeons performed heart transplant number 100, when they reported near 90% survival rates for the first year, and 30% after 14 years.

Despaigne was born with a rheumatic cardiopathy that provoked enlargement of the vital organ, and made transplantation his only hope for life. A multidisciplinary team headed by eminent Cuban cardiologist Dr. Noel González, performed the 10-hour surgery in Havana’s Hermanos Ameijeiras Hospital, and the institution’s Transplant Team continues to follow Despaigne’s case with cardiologists in his native Las Tunas.

Despaigne has lived virtually a normal life since the transplant, regularly riding his bicycle, and spending time with his five-year-old daughter Elba Daniela. Dr. Roberto Rabert, one of the Las Tunas team of cardiologists caring for Despaigne, describes his condition as stable, and his chronic hypertension under control.

The number of heart transplants in Cuba dropped during the nineties, a result of the island’s economic crisis, but recovered its rhythm in 2000, according to Dr. González.

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Running for a Cure: Terry Fox Inspires Cuba

By Conner Gorry

At the tender age of 18, Canadian Terry Fox had his right leg amputated above the knee due to bone cancer. While someone else might lament such a fate, struggling against the disease before succumbing, Terry Fox fought against all odds and expectations to challenge cancer. In 1980, outfitted with a prosthetic leg, he kicked off his Marathon of Hope in Newfoundland, Canada, with the goal of running across the country — over 6,000 miles — to raise awareness and money for cancer research. After 143 days of running an average of 26 miles a day, he was hospitalized and died on June 28, 1981.

On March 20th, 25 years after Terry Fox’s heroic effort, nearly one million Cubans across the island set off in the world’s second-largest annual Terry Fox Run Against Cancer. Designed to promote a healthy lifestyle, educate about cancer and raise funds for research, the event is hosted in over 50 countries worldwide; Cubans have embraced the cause with verve, making the island run the biggest outside of Canada.

Launched in Havana in 1998, Cuban athletic and health officials have prioritized the run as a way to encourage healthy practices and raise funds for the national Institute of Oncology and Radiobiology. Cancer is the second most frequent cause of death in Cuba after heart disease; 30% of those deaths are tobacco-related (lung cancer tops the list), and another 30% are due to poor diet. Furthermore, despite ongoing advances in key health indicators including infant mortality and life expectancy, cancer deaths in Cuba increased by 2% between 1990 and 2000.

The Cuban Ministry of Health (MINSAP) wants to change that. Since 2003, the Terry Fox Run Against Cancer has been held in every municipality countrywide to publicize cancer’s causes, effects and the best prevention measures people can take against the disease. Indeed, prevention is the cornerstone not only of the Cuban public health system as a whole, but also in the country’s fight against tobacco-related cancer: in February, Resolution 335/04 took effect, banning smoking on buses and trains, in baseball stadiums, offices, restaurants and all other public spaces.

MINSAP and the Sports Institute work closely with the Canadian Embassy to organize and promote the run, including hosting cultural activities to raise money for the Institute of Oncology and Radiobiology. This year, a gala concert starring Cuban jazz great Chucho Valdés, Canadian trombonist Hugh Fraser and saxophonist-flautist Jane Bunnett lit up Havana’s Teatro Nacional while raising funds for breast and uterine-cervical cancer research. In her welcoming remarks, Canadian ambassador Alexandra Burgailiskis lauded the Cuban people and government for their support in the fight against cancer, citing them as an example of the triumphant will embodied by Canadian hero Terry Fox.
MEDICC Review would like to extend a warm welcome to all the participants in

NEPHROLOGY 2005
May 14-18
Plaza América Convention Center, Varadero, Cuba.

We hope you enjoy this complimentary issue of MEDICC Review.

MEDICC Review aimerait envoyer une bienvenue chaleureuse aux participants dans

NEPHROLOGIE 2005
Du 14 au 18 Mai
Palais des Congrès Plaza América, Varadero, Cuba

Nous espérons que vous trouverez intéressant ce numéro que nous vous proposons.

MEDICC Review les desea una cordial bienvenida a todos los participantes en

NEFROLOGÍA 2005
14-18 de Mayo
Centro de Convenciones "Plaza América", Varadero Cuba

Esperamos que este ejemplar de cortesía de MEDICC Review sea de su interés.

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