Chapter 14. Kidney Disease

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Boxes: 2
Figures: 3
Maps: 0
Tables: 5
Word count: 11,850, including 3,580 in references
Annexes: table 1 = 138 words; annex table 2 = 173 words
Note: Table 3 = 288 words; table 4 = 825 words
Graphics requiring permission: 2

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Introduction

Deterioration in kidney function, whether acute or chronic, can lead to substantial morbidity and mortality. Acute kidney injury (AKI) is a powerful indicator for in-hospital mortality; those who survive face increased length and cost of hospitalization. Some individuals with chronic kidney disease (CKD) develop progressive renal dysfunction and require costly therapy with dialysis and/or transplant. Even more often, individuals with CKD face high risks for cardiovascular events, anemia, and fractures.

This chapter reviews current data on the epidemiology and trends in the etiology of AKI, CKD, and end-stage renal disease (ESRD), with a focus on low- and middle-income countries (LMICs). We also review management of these conditions, highlighting several interventions—treatment for AKI, screening for CKD, and modality choice for ESRD—with available data on cost or cost-effectiveness.

Acute Kidney Injury

The Condition

Incidence

AKI occurs commonly, although quantifying its exact burden has been challenging. Prior to 2004, no standardized definition existed. Symptoms do not occur unless severe disease develops. The causes vary widely according to setting—whether it is acquired in hospitals or in communities—and establishing practice patterns for screening is difficult. Community-based studies of prevalence illustrate the wide variation in estimates of AKI that are subject to definition and population; studies report annual incidence rates ranging from 22 to 175 per million population (Himmelfarb and Ikizler 2007).

Recently, however, the nephrology community established standardized criteria for a case definition of AKI, and evidence indicates that an increasing number of epidemiology reports relies on this definition (Mehta et al. 2015). First released in 2004(Bellomo et al. 2004) and updated in 2007 (Mehta et al. 2007) and 2012 (Palevsky et al. 2013), these definitions emphasized recognizing early signs of kidney injury, with attention to relatively small changes from baseline serum creatinine or expected urine output—since even these small changes are linked with a substantially increased risk for in-hospital mortality (Online annex table __A.1) (Chertow et al. 2005).

Annex table A. 1. Kidney Disease Improving Global Outcomes (KDIGO) Criteria for AKI Severity

AKI Stage	Definition		Treatment	Incidence (%)*
	Serum creatinine	Urine (ml/kg/hr)		
Risk	1.5x increase in creatinine	< 0.5ml/kg/h for 6 hours	Treatment of underlying cause of AKI	11.5
Injury	2x increase in creatinine	< 0.5ml/kg/h for 12 hours	Treatment of underlying cause of AKI	4.8
Failure	3x increase in creatinine OR > 0.5mg/dl if baseline creatinine is higher than 4.0mg/dl	< 0.3 ml/kg/h for 24 hours OR anuria for 12 hours	Treatment of underlying cause of AKI AND renal replacement therapy provision:	4.0

			- conventional hemodialysis OR - low-flow dialysis therapies OR - peritoneal dialysis	
Loss	Loss of complete renal function > 4 weeks		Renal replacement therapy	2.3
End-stage	End-stage renal disease			
Sources: * Incidence calculated using random effects model meta-analysis of pooled studies, data from (Susantitaphong et al. 2013). *Note*: AKI = acute kidney injury.				

Standardizing 130 studies to the Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI, a recent extensive global meta-analysis estimates that one in four adults and one in three children throughout the world suffer from AKI during hospitalized care; about 10 percent of these patients develop AKI severe enough to require dialysis (Mehta et al. 2015, Hoste and Schurgers 2008, Susantitaphong et al. 2013). The overall AKI incidence rate among adults and children was 23.2 percent (CI 21.0 to 25.7%), with the highest incidence rate of 31.7 percent occurring in the critical care setting [95% CI 28.6 to 35.0%]. The severe AKI incident rate was 2.3 percent. Data available on the incidence rate of community-acquired AKI were scarce; only seven studies reported this data; however, the rate was relatively lower than that of hospital-acquired AKI at 8.3 percent (95% CI 1.6 to 33.0%) (Susantitaphong et al. 2013).

This analysis also had only two studies from LMICs. However, a recent update capturing more data from Africa, Asia, and Latin America reported comparable incidence of AKI in these regions, compared with HICs (Mehta et al. 2015).

Mortality

Mortality from AKI in HICs has traditionally been reported to be higher than in LMICs, but two more recent reports indicate taht at least among patients with severe AKI requiring dialysis, mortality rates in LMICs are equivalent or higher. A prospective study of AKI in patients hospitalized in intensive care units collected data from Brazil, China, and India, three middle-income countries (MICs); findings indicated that patients in MICs experienced two-fold higher odds of mortality and non-recovery of renal function, despite having lower severity of illness, compared with patients in HICs (Bouchard et al. 2015). In the ISN 0by25 Global Snapshot study, a prospective cross-sectional study in 72 countries of pediatric and adult patients who met criteria for AKI during late 2014, mortality at seven days after AKI varied from 11.5 percent in patients from LMICs to 13.6 percent in upper middle-income countries(Mehta RL). Notably, mortality was significantly different in dialyzed versus non-dialyzed patients, 17 percent and 9 percent, respectively. Single-center studies from LMICs have reported a large variation in mortality from AKI requiring dialysis, likely reflecting not only the lack of equipment but also the variable levels of expertise (table __.1).

Table __.1. Selected Studies with Mortality Estimates for AKI

Author, Year	Study population	Overall Mortality (percent of patients with AKI)	Mortality for AKI cases receiving dialysis (percent)
Low- and Middle-Income Countries			
(Susantitaphong et al. 2013)	Pooled global mortality rate	8.0–22.6 *	n.a.

(Mishra et al. 2012)	Children receiving PD	n.a.	36.8
(Ademola et al. 2012)	Children receiving PD	n.a.	30
(Bagasha et al. 2015)	Patients with sepsis at a Ugandan teaching hospital	21	100
(Ponce et al. 2012)	Patients receiving PD for AKI	n.a.	57.3
(Trang et al. 1992)	Patients receiving PD for AKI	n.a.	26.0
(Kilonzo et al. 2012)	PD for AKI in children (20 percent) and adults (80 percent)	n.a.	20.0
Mehta, in press	Pooled global mortality rate from community and hospital acquired AKI, seven-day mortality	11.5***	17***
High-Income Countries			
(Susantitaphong et al. 2013)	Pooled global mortality rate	20.9	49.4**
(Waikar et al. 2006)	In-hospital mortality, 1998-2002	20.3	28.1
(Talabani et al. 2014)	Community-acquired AKI, three-month mortality	16.5	N/A

Notes:
AKI = acute kidney injury; PD = peritoneal dialysis.
* Represents one study from low-income countries, and one from low- and middle-income countries.
**Of the 31 studies pooled for this estimate, two were from low- and middle-income countries.
*** From 1,153 AKI patients from low- and lower-middle-income countries.

Etiology

Although rigorous registry data are lacking, experts suggest that the incidence of community-acquired AKI—that is, patients presenting to the hospital after developing symptoms of kidney dysfunction, rather than presenting with a systemic illness that during its treatment course is associated with AKI (hospital-acquired AKI)—is higher in LMICs than HICs. Severe systemic diseases, such as sepsis or major surgical procedures, cause the majority of cases of AKI in HICs and in urban areas of LMICs. Some community-acquired reasons for AKI are more common in LMICs: obstetric complications; toxins, including snake venom; diarrheal illness; advanced HIV/AIDS; leptospirosis; and malaria.

In Africa, nephrologists reported that major causes of AKI are related to the burden of HIV/AIDS, malaria, leptospirosis, and diarrheal diseases (Lameire and others 2013; (Prakash et al. 2015, Naicker,

Aboud, and Gharbi 2008, Lameire et al. 2013) More than 50 percent of adults with advanced HIV/AIDS or severe malaria can develop AKI (Lameire et al. 2013). Noninfectious causes specific to LMICs include obstetric and surgical complications, such as severe hemorrhage or late diagnosis of eclampsia, as well as widespread use of traditional herbal remedies or nonsteroidal anti-inflammatory agents (Naicker, Aboud, and Gharbi 2008, Luyckx and Naicker 2008). Such community-acquired AKI more likely afflicts a younger age group, and especially in cases of malaria or diarrheal illness, exhibits seasonal peaks during rainy seasons (Cerda et al. 2008, Lameire et al. 2013).

Interventions and their effectiveness

AKI management largely depends on etiology and severity. Treatment algorithms in HICs recommend optimizingvolume using crystalloid solutions until clinical dehydration is corrected followed by vasopressor support to maintain perfusion pressure (Kellum, Lameire, and Group 2013). In conjunction with this approach, treatment of the underlying cause of AKI, such as antibiotics for infection, and avoidance of nephrotoxic medications or procedures often leads to resolution of mild-to-moderate AKI. In HICs, the availability of intensive care units, adequate nursing staffing, and rapid turnaround laboratory facilities allow for frequent and close monitoring of urine output and serum creatinine. Relatively prompt interventions to ameliorate AKI are performed. If AKI progresses to severe renal failure despite these measures, temporary dialysis may be initiated, either to treat volume and electrolyte imbalances or to remove toxins (See Box ___.1 for an example in LMIC context). Continuous hemodiafiltration and intermittent hemodialysis are the modalities of choice in HICs, although a recent meta-analysis highlighted equivalent survival in patients receiving peritoneal dialysis (PD) versus hemodialysis or continuous hemodialfiltration (Chionh et al. 2013).

This level of care is not available in most LMICs. The limitations of diagnosis and treatment for advanced AKI are particularly stark in rural areas, but they are also demonstrated in urban university-based hospitals (Bouchard and others 2015; Cerda and others 2008). Data on missed or delayed diagnosis of AKI in LMIC are nonexistent; by their nature, reports on epidemiology of AKI must apply screening criteria that may not be used in standard practice in LMICs. However, studies have confirmed not only a lack of provision of dialysis or transplant, but also lack of intensive care units as crucial gaps in care (Bagasha et al. 2015). To address these gaps, the International Society of Nephrology (ISN) has begun an initiative “0 by 25,” with the objective of eliminating preventable death from AKI by 2025 by calling for global strategies that permit timely diagnosis and treatment, including dialysis, of potentially reversible AKI, with particular emphasis on LMICs (Mehta et al. 2015, Remuzzi and Horton 2013).

Box __.1: Case Study: AKI treatment with Peritoneal Dialysis in Tanzania

An AKI treatment program started in 2007 at Kilimanjaro Christian Medical Centre in Tanzania is a leading example of renal replacement therapy provision for AKI in a low-income country (Burki 2015). The program employs peritoneal dialysis.

The program was developed through the support of the International Society of Nephrology and Sustainable Kidney Foundation, who funded training of physicians and nurses from Tanzania to receive training in Brazil for peritoneal dialysis catheter insertion technique and prescription (Callegari and others 2012; Callegari and others 2013; (Kilonzo et al. 2012, Callegari et al. 2013, Callegari et al. 2012). The program, directed by Dr. Karen Yeates of Queen’s University, Canada, administered peritoneal dialysis to 32 patients with AKI. The AKI treatment costs are low: approximately US$150-US$400 for the duration of in-hospital treatment, ensuring sustainability once the center assumes total program management (Burki 2015).

One of the major lessons has been that nephrologists are not essential for the successful development of such programs. Skilled internists and nurses willing to be trained in peritoneal dialysis delivery can achieve satisfactory results (Burki 2015).

Cost and Cost-Effectiveness of Interventions

AKI-related health expenditures reflect costs associated with renal replacement therapy, as well as prolonged hospital stay and increased complexity of care once kidney function has been compromised during illness course, even if compromise of renal function is modest (Chertow et al. 2005, Rewa and Bagshaw 2014):

- Prolonged hospitalization
- Intensive case unit services
- Dialysis
- Increased monitoring and intervention
- Increased risk of re-hospitalization.

A global meta-analysis estimated that 45 percent of represented countries spend 5 to 10 percent of total health expenditures on AKI; 49 percent spend less than 10 percent (Susantitaphong et al. 2013).

The cost-effectiveness of dialysis provision depends largely on the post-hospitalization survival of patients. The SUPPORT study assessed the cost effectiveness of initiating dialysis in seriously ill hospitalized patients in the United States. Only 27 percent of patients survived after six months; the cost per quality-adjusted life year gained was calculated at US$128,200 (Hamel et al. 1997). A cross-sectional study in Finland to assess the cost utility of acute renal replacement therapy from the societal perspective reported the intervention to be cost-effective only if survival exceeded a year (Laukkanen et al. 2013). The study involved a five-year follow-up of patients who received acute renal replacement therapy (RRT) in a largely ICU-based setting.

Since the demographics of AKI skew toward a younger population with lower illness severity, it is likely that the benefits of dialysis provision are greater in LMICs (Anand, Cruz, and Finkelstein 2015); Bouchard and others 2015). However, few cost data are available. One report from Tanzania found that cost of one live saved using acute peritoneal dialysis was US$370 (Cullis et al. 2014). George and others (2011) reported that the equipment and solution costs of peritoneal dialysis were Rs 3009 (US$47), approximately 40 percent of continuous hemodialysis filtration costs (Rs 7184 [US$112]), with equivalent survival.

Recommendations for Policy Makers in LMICs

Although the current understanding of AKI in LMICs is limited, the nephrology community generally agrees on the following (Mehta et al. 2015):

- Known incidence is similar to that in HICs
- Community-acquired causes are more common than in HICs
- Affected patients are younger than in HICs
- Lack of intensive care units and access to acute dialysis results in high mortality rates.

This consensus is largely drawn from expert opinions or single-center studies; additional studies are required to estimate the burden, etiology, and mortality related to AKI in LMICs.

If the above consensus is backed by data, the prevention of AKI (table __.2) may play a more crucial role in LMICs. Management algorithms taking into account most common region-specific causes are crucial in areas with limited staffing of trained physicians. When the need for dialysis arises, temporary peritoneal dialysis—a less technologically demanding and less costly modality—can be used for both pediatric and adult acute cases. The International Society of Peritoneal Dialysis has published guidelines to standardize the provision of acute peritoneal dialysis (Cullis et al. 2014). Successful programmatic implementation of this modality in terms of training staff, acquiring dialysis equipment, and prescribing dialysis appropriately has occurred in third-level centers in Benin, Cambodia, Ghana, Sudan, and Tanzania (Finkelstein et al. 2014, Wilkie 2014). The challenge of scalability and managing patients who do not recover renal function and require long-term dialysis remains (Kilonzo et al. 2012).

Table __.2. Prevention and Management of AKI in LMICs

Recommended Intervention	Potential Benefit
Prevention or management at community level	
Improve access to, and quality of, drinking water and sanitation	Prevent AKI related to diarrheal illness, kidney stones, and volume depletion in strenuous working conditions
Educate health care workers, pharmacists, and general populations about nephrotoxic medications and herbs	Reduce AKI related to heavy NSAID, illegal alcohol, or herbal toxin use
Involve local health care workers in the identification of patients at risk of AKI	Prevent or limit exposure to environmental risk factors for AKI, such as parasites, infection-carrying vectors, and obstetric complications
Educate and train nonphysicians, such as nurses or clinical officers, or non-health professionals to locally manage AKI, especially with telemedicine support	Limit the progression of AKI to more severe stages requiring dialysis or replacement therapy
Prevention or management at hospital level	
Improve perinatal care at primary-level hospitals	Reduce AKI related to peripartum hemorrhage or pre-eclampsia
Enhance region-specific understanding of common causes of AKI at first- and second-level hospitals	Provide rapid treatment of underlying causes of AKI
Implement protocols for intensive or intermediate care at first- and second-level hospitals	Resolve mild-to-moderate AKI via rapid fluid resuscitation, vasopressor support, and antibiotic administration
Provide training in peritoneal dialysis provision for AKI at second-level hospitals	Treat severe AKI by training non-nephrology physicians in peritoneal dialysis catheter insertion and prescription; enable wider availability for dialysis for severe AKI
Create referral centers for provision of hemodialysis (intermittent or continuous) for patients in whom peritoneal dialysis is contraindicated	Select individuals with severe AKI who need specialized care and efficiently allocate resources for dialysis

Source: Authors
Note: AKI = acute kidney injury; NSAIDs = nonsteroidal anti-inflammatory drugs.

Chronic Kidney Disease and End-Stage Renal Disease

The Condition

Epidemiology of CKD
CKD is diagnosed when an individual has evidence of persistent kidney dysfunction, as reflected by albuminuria and/or reduction in estimated glomerular filtration rate (eGFR)[†]. Identifying individuals with CKD arguably facilitates treatment to reduce cardiovascular events and slow the progression to ESRD (Levey and Coresh 2012).

However, guidelines to streamline CKD diagnosis have generated controversy, due to their reliance on GFR (online annex table 2) (Levey et al. 2003, Kidney Disease: Improving Global Outcomes Work Group 2012). Older adults who have isolated modest eGFR reductions may have kidney function at the lower end of the normal-for-age range (Wetzels et al. 2007), creating the potential for false positives and overutilization of medical resources (Moynihan, Glassock, and Doust 2013, Poggio and Rule 2009). Most cross-sectionally obtained prevalence estimates fail to fulfill the criteria of repeating assessment at three months to determine persistence (Plata et al. 1998). Finally, interpretation of albuminuria requires caution in LMICs, where hygiene, malnutrition, and dietary habits may impact urinary excretion of albumin and creatinine.

Online Annex table 2. Kidney Disease Improving Global Outcomes (KDIGO): Stages of Chronic Kidney Disease

eGFR categories (ml/min/1.73m^2)			Albuminuria categories (mg/g)		
			A1	A2	A3
			< 30 mg/g	30-300 mg/g	≥ 300 mg/g
G1	Normal or high	≥ 90			
G2	Mildly decreased	60-89			
G3a	Mildly to moderately decreased	45-59			
G3b	Moderately to severely decreased	30-44			
G4	Severly decreased	15-29			
G5	Kidney failure	<15			

Source: Based on http://kdigo.org/home/guidelines/ckd-evaluation-management/.

Note: Green = low risk; yellow = moderately increased risk; orange = high risk; red = very high risk.
In response to criticism of the first published guidelines (NKF/KDOQI 2002), these guidelines attempt to move away from heavy reliance on estimated glomerular filtration rate and incorporate prognosis as predicted by accompanying albuminuria (Kidney Disease: Improving Global Outcomes Work Group 2012). For example, individuals with eGFR 45-59 m/min/1.73 m^2 without albuminuria are labeled as being at moderately increased risk for adverse events related to CKD, compared to individuals with eGFR 45-59ml/min/1.73m^2 and with albuminuria > 300 mg/g who are recognized to be at very high risk.
eGFR = estimated glomerular filtration rate.

With these caveats in mind, we make the following interpretation from available population-based prevalence studies (table __.3):

- CKD prevalence is understudied in LMICs.
- CKD prevalence in LMICs approaches that of HICs.
- Earlier stages of CKD—albuminuria alone—are common in LMICs, unlike HICs, where modest eGFR reductions with or without albuminuria (CKD stage 3) predominate.

At the same time, individuals with CKD in LMICs remain at high risk of adverse events. Notably, albuminuria has been associated with a linear and sizable increase in risk for all-cause mortality and cardiovascular events, starting at urine albumin-to-creatinine ratios above 10 mg/g (Chronic Kidney Disease Prognosis et al. 2010). Risk for end-stage renal disease is 4-11 fold higher among individuals with albuminuria (Chronic Kidney Disease Prognosis et al. 2010).

Table __.3. Selected Population-Based Studies Reporting Prevalence of CKD
[*table sources need to be added to references list*]

Study	Setting	N	Equation for eGFR	Measure of proteinuria	Assessment of persistence	Overall CKD (%)	eGFR < 60 (%)
Coresh et al.	U.S. NHANES	13,233	MDRD	UACR	UACR repeated at 2 weeks in subset	13	8
Hallan et al.	Norway HUNT II	65,181*	MDRD	UCAR	UACR repeated on 3 consecutive samples	11	5
Otero et al.	Spain EPRICE	2,746	MDRD	UCAR	No	9	7
Imai et al.	Japan	574024	Japanese eq	Dipstick proteinuria	No	13	11
Chadban et al.	Australia AusDiab	11,247	CG	UPCR	No	16	11
Otero et al.	Spain	2,746	MDRD	UACR	No	9	7
Amato et al.	Urban Mexico	3,564	CG	Dipstick proteinuria	No	17	8.5
Zhang et al.	China	47,204	MDRD	UACR or UAC	No	11	2
Ingsathit et al.	Thai SEEK	3,459	MDRD	UACR	No	17.5	9
Anand et al.	India CARRS	9,797	CKD Epi	UACR	No	9	3
Stanifer et al.	Tanzania, urban/rural	481	MDRD	Albustix	Yes	7	1.7
Kaze et al.	Cameroon urban/rural	439	CKD EPI	UACR	Yes	13.2	2.5
Seck et al.	Northern Senegal	1,037	CKD	Dipstick	No	6.1	3.4

* = UACR re-performed in a 5 percent sample.

Note: Most studies did not repeat assessment of eGFR or albuminuria. Most studies used the MDRD equation, which is known to underestimate GFR among individuals without kidney disease, a third reason for concerns about overdiagnosis of CKD. Developed in 2009, the CKD-EPI equation is more specific, but its applicability to non-Caucasian ethnic groups is unclear.

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MDRD = Modified Diet in Renal Disease; CKD-EPI-Chronic kidney disease Epidemiology Collaboration; CG = Cockcroft Gault; UACR = urine albumin-to-creatinine ratio; UAC = urine albumin concentration.

Epidemiology of ESRD

ESRD is rare. About 2 million people are undergoing renal replacement therapy (dialysis or kidney transplant) worldwide, with a prevalence of 300 per million adult population or 0.03 percent, compared with prevalence estimates in the range of 7-15 percent for earlier stages of CKD (Grassmann et al. 2005, Anand, Bitton, and Gaziano 2013, Thomas et al. 2015). Most individuals receiving renal replacement therapy live in HICs (Grassmann et al. 2005). The latest Global Burden of Disease estimates from the World Health Organization note that 1.8 percent and 1.1-1.8 percent of deaths in HICs and LMICs, respectively, are attributable to kidney disease, with the cause of death presumably complications of ESRD.

Currently available data only capture information on patients who have access to renal replacement therapy, not all those who develop ESRD. In HICs, these numbers are roughly equivalent, since most patients who develop ESRD are diagnosed and offered therapy. In LMICs, however, renal replacement therapy incidence is not a proxy for ESRD incidence, because individuals may die prior to or immediately after diagnosis, or they may withdraw from therapy because they cannot pay for it (Couser et al. 2011).

Two recent analyses comparing renal replacement therapy use with projected ESRD prevalence have highlighted a large disparity (Anand, Bitton, and Gaziano 2013, Liyanage et al. 2015); fewer than five percent of patients projected to have ESRD access therapy in China, India, and Nigeria (Anand, Bitton, and Gaziano 2013). The provision of renal replacement therapy tracks closely with a country's gross national product, rather than the prevalence of risk factors.

Trends in Prevalence and Etiology of CKD and ESRD

Despite concerns about accurate diagnosis, most experts agree that CKD is a rising concern worldwide due to the skyrocketing prevalence of its major correlates: diabetes and hypertension. As noted in Chapters 2 and 13, LMICs are projected to experience the largest percentage increases in the prevalence of diabetes and hypertension (Hossain, Kawar, and El Nahas 2007). Individuals in LMICs are more likely develop end-organ damage, including progressive CKD, due to delayed diagnosis and poor management of these conditions. In a study of individuals with diabetes in Cambodia, more than 50 percent had CKD (Thomas et al. 2014), compared with about one third in the United States (de Boer et al. 2011). Not surprisingly, these diseases are an increasingly common cause of ESRD in LMICs. In 2011, 28 percent of cases of ESRD in Brazil were attributed to diabetes, compared with 8 percent in the mid-1990s; 35 percent were attributed to hypertension, compared with 15 percent in 2002 (Sesso Rde et al. 2012, Oliveira, Romao, and Zatz 2005).

Unusual causes of CKD, including stones, environmental toxins, and infectious diseases, are also concentrated in LMICs. It is increasingly apparent that CKD in LMICs is a multi-hit condition due to interacting factors, such as poverty and social deprivation, poor sanitation and hygiene, exposure to water- and food-borne toxins, pollution, and infectious diseases.

Stone-related kidney disease is also relatively more important in certain regions. In HICs, 3 percent of cases of ESRD are attributed to obstructive uropathy (Jungers et al. 2004); in countries along the "stone-belt"—a region encompassing North Africa and South and Southeast Asia—up to 6-11 percent percent of cases of ESRD are attributed to obstructive uropathy (Jha 2009). Hot climates predisposing to volume depletion, low urine output, low potassium diets, and chewing of calcium hydroxide-containing betel leaf increase the risk for stone formation (Lopez and Hoppe 2010). Limited access to treatment increases the risk for CKD and ESRD.

Individuals in LMICs also experience higher risk for CKD related to environmental toxins, such as lead, arsenic, cadmium, and aristolochlic acid. Public health experts from Sri Lanka and west coast of Central America reported that scores of agricultural workers are being diagnosed with CKD unaccompanied by diabetes or hypertension (box __.2) As yet there many unknowns about this phenomenon, including whether the same disease entity is afflicting workers in both regions, and whether strenuous work in high heat may be a major contributing factor.

Box __.2 Case Study: Investigating Kidney disease in Farm Workers

Since early 2000s a form of chronic kidney disease unaccompanied by diabetes or significant hypertension has been reported primarily in rice paddy farmers in the dry zone of Sri Lanka (Chandrajith et al. 2011), and sugarcane workers in lowlands of Nicaragua and El Salvador (Weiner et al. 2013). Estimates of mortality are high. In 2009, kidney disease was the second largest cause of death among men in El Salvador (Wesseling et al. 2013). Some distinguishing features of the disease have been described: it afflicts middle-age men more so than women, lacks heavy proteinuria, and tends to progress to end-stage renal disease. On kidney biopsy, pathologists note a tubulo-interstitial nephritis (Nanayakkara et al. 2012, Wijkstrom et al. 2013).

A rural low-land community in Nicaragua is referred to as "La Isla de las Viudas," (The Island of Widows), because of the high rates of death among men in the village due to renal failure. One of the non-governmental agencies working to address this problem, La Isla Foundation, is based in this region. The La Isla Foundation has extended its efforts beyond activism to generate media attention and to support collaborative research in the field. In addition, scientists from a variety of institutions including Boston University, National Autonomous University of Nicaragua at Leon, and the University of Colorado in Denver are investigating potential triggers for kidney disease. A Consortium for the Epidemic of Nephropathy in Central America and Mexico has been formed to help researchers communicate and coordinate.

One prevailing hypothesis for the cause of this epidemic is recurrent dehydration due to strenuous work in high heat conditions (Roncal Jimenez et al. 2013). However, there is widespread belief among local populations in Meso-America and in Sri Lanka that exposure to agrochemicals is at least partly responsible for the occupational nature of this form of CKD (Jayasumana et al. 2015). An as yet undefined infection also remains an important consideration (Murray et al. 2015).

Most afflicted by the disease earn their livelihood from agricultural work; a diagnosis of progressive CKD is disabling for them and their family. There is little to no provision for dialysis therapy in these regions, lending great urgency to identifying an etiology and thereby preventing the disease.

Interventions and their Effectiveness

Screening

Major primary care and nephrology guidelines in HICs do not advocate universal screening for CKD. The NKF/KDOQI recommends first evaluating individuals for risk factors for CKD during routine clinical encounters, and if risk is determined, then further evaluating them for serum creatinine and urine abnormalities. The risk factors include age; diabetes; hypertension; autoimmune disease, such as lupus; urinary tract abnormalities, such as infections, stones, and neoplasia; low birth weight; and exposure to toxins, such as drugs, environmental agents, or infections. In practice, physicians target screening to individuals with diabetes or hypertension. Since serum creatinine and automated reporting of eGFR is often part of the routine studies in primary care, even individuals without specific risk factors for CKD are recognized at an early stage (Wyatt and others 2007).

The adoption of a targeted screening strategy needs reassessment in LMICs, given the lack of self-awareness of underlying risk factors for CKD. For example, in a community-based sample from urban India, individuals with and without knowledge of diabetes had similar prevalence of CKD (Anand et al. 2015). Accordingly, selecting high-risk individuals for CKD screening may not be feasible.

Prevention of ESRD

Pharmacotherapy for CKD associated with Diabetes or Hypertension. Nephrologists employ angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) as the primary medical therapy to delay the progression to ESRD. Data from several randomized clinical trials have shown that these medications can slow the progression of CKD among individuals with proteinuric (diabetic and non-diabetic) kidney disease, with risk reduction approaching 40 percent for a composite endpoint of doubling of serum creatinine or ESRD (Kshirsagar et al. 2000). A trial in China replicated these findings for individuals with proteinuria advanced renal insufficiency (Hou et al. 2006). Some evidence indicates that even among individuals with CKD and hypertension without significant proteinuria, the use of ACE inhibitors may delay the progression of CKD beyond the effects achieved by other standard antihypertensive agents (Wright et al. 2002). Whether the effect of ACE inhibitors is totally independent of improved blood pressure control has been debated. These medications, which are relatively inexpensive in their generic form, are well-tolerated but require laboratory monitoring for hyperkalemia and/or significant change in serum creatinine among older patients and those with advanced CKD due to associated risk for AKI.

Pharmacotherapy for Glomerular Diseases. Chronic kidney disease associated with diabetes or renovascular disease is often diagnosed only with screening. Individuals with glomerulonephritis, in contrast, often have classical symptoms, such as edema, hematuria, or arthralgias, and are referred to nephrologists for immunotherapy. Steroids are the initial choice of therapy for many glomerular processes: minimal change disease, membranous nephropathy, focal segmental glomerulonephritis, and IgA nephropathy. Newer steroid-sparing therapies, such as calcineurin inhibitors, are used in individuals at serious risk for adverse events related to steroids or for maintenance therapy. Cyclophosphamide had been the mainstay of therapy for severe glomerulonephritis due to lupus or vasculitis. Mycophenolate mofetil (Ginzler et al. 2005) and rituximab (Stone et al. 2010) have been shown to be equally efficacious in each disease, respectively.

Race or ethnicity may affect the efficacy of immunotherapy. African-American and Hispanic individuals with lupus reportedly respond better to mycophenolate mofetil than to cyclophosphamide (Isenberg et al. 2010). Initial clinical trials from China reported the efficacy of mycophenolate mofetil in individuals with

IgA nephropathy, but these results have not been replicated in clinical trials in Belgium and the United States (Floege and Eitner 2011).

Data on availability and/or appropriate use of these pharmacotherapies in LMICs are limited. One study from Mexico reported that a third of primary care physicians working in the public sector scored in the "very low knowledge" category in a competence evaluation of diabetic kidney disease (Martinez-Ramirez et al. 2006). Only 50 percent of patients with diabetes underwent simple screening for kidney disease; fewer than 20 percent of patients with proteinuria had been placed on ACE inhibitor in a third-level center in Nigeria (Agaba et al. 2009).

CKD-Specific Programs in LMICs. We conducted a PUBMED and EMBASE systematic search to capture any programs designed specifically to improve care of patients with CKD or ESRD in LMICs. Of the 292 captured by the search, we culled 18 with available full-text in English for further review; articles were excluded for not being applicable to LMICs, being presented in abstract only at conferences, or not describing a specific intervention. After excluding reports that were too general or did not capture any outcomes, we found nine studies that described CKD care programs in LMICs (table __.4). Although the data on evaluation of these programs was of poor to fair quality, an emerging theme in these reports is the importance of education of primary care physicians in identifying and treating patients at risk for CKD progression.

Table __.4. Summary of Programs Targeted to Caring for Patients with CKD in LMICs

Authors	Country	Intervention	Level	Outcomes
(Mastroianni-Kirsztajn, Bastos, and Burdmann 2011)	Brazil	"Previna-se": a campaign by Brazilian society of nephrology to increase awareness of CKD among health professionals and public	National	• In 2009, 700 local programs registered for educational campaigns • Generated pamphlets and videos for PCPs and public • Attempted to standardize reporting of GFR • Undertook several screening campaigns in Saö Paulo
(Zhang et al. 2008)	China	Established a renal management clinic study at Peking University that incorporated nephrologists, dietician, and nurses	Third-level hospital	• Challenges in follow up, with 10 percent of patients with advanced CKD not returning for follow up • Despite creation of multidisciplinary clinic, lack of involvement of nurses or dieticians
(Jiang and Yu 2011)	China	Created 12 satellite peritoneal dialysis clinics to an academic hospital. Used standardized protocols for training staff Q6 monthly staff meetings at academic hospital.	Third-level and first-level care partners	• Increased capacity • Decline in peritonitis rate (1 episode/39.4 to 1 episode/46.2 patient months) • Fewer patient drop outs, from 28 to 18 percent per year
(Wong, Chow,	China	Randomized peritoneal	Tertiary	• With involvement of nurses,

and Chan 2010)		dialysis patients to renal and general nephrology nurse follow up vs usual care (physicians only)	hospital	improved diet adherence, symptom control and quality of life
(Mani 2010)	India	Developed a protocol for titration of ACE-I/ARB among patients with CKD who lived remotely from the specialists; instructions were faxed after patients relayed results of protocol labs	Community	• Among patients who were able to follow the protocol, rate of decline in kidney function was significantly slower • Able to perform titration despite only 6 or 12 month of follow up from patients
(Cortes-Sanabria et al. 2008)	Mexico	Randomized PCPs to usual care vs 6 months of education about CKD in patients with type 2 diabetes	Primary care	• Improved PCP clinical competence • Better controlled BP and albuminuria, with higher doses of ACE I/ ARB used among patients of educated PCPs
(Cueto-Manzano, Martinez-Ramirez, and Cortes-Sanabria 2013)	Mexico	Prospective study of patients with type 2 diabetes and early CKD assigned participating in multi-disciplinary (educated PCP, dietician, physical therapist, social worker) versus usual care	Primary care	• Improved medication compliance • Improved BP, hemoglobin A1c, and waist circumference in patients with multidisciplinary care
(Edefonti et al. 2010)	Nicaragua	Partnership between Milanese and Nicaraguan hospitals to create a pediatric nephrology program	National	• Trained three pediatric nephrologists and two pathologists • Created a network of PCPs in six other regions; these PCPs have access to basic diagnostics and could streamline referral to main hospital • Covers 61 percent of pediatric population
(Schwedt et al. 2010)	Uruguay	A national renal health care program that focused on education of both PCPs and nephrologists, with referral to recommended at advanced CKD	National	• Post implementation, patients getting care from PCPs and from nephrologists demonstrated improved BP and lipid control
(Sharma et al. 2014)	Nepal	An intervention program in resource-poor setting of eastern Nepal with cheap antihypertensive, antidiabetic or renoprotective (ACE) drugs	Rural communities of eastern Nepal	• 76 percent on active monitoring after three- year follow-up • Improved BP and glycemic control • 63 percent of participants

				with dipstick proteinuria ≥1+ at baseline decreased to normal values • 48 percent of participants with eGFR <60 ml/min/1.73 m^2 at baseline improved renal function

Note: ACEI/ARB = angiotensin converting enzyme inhibitors/angiotensin II receptor blockers; BP = blood pressure; CKD = chronic kidney disease; GFR = glomerular filtration rate; PCP = primary care physicians; LMICs = low-and middle-income countries.

Treatment of ESRD

Survival on dialysis. Survival on dialysis—equivalent for hemodialysis and peritoneal dialysis—is generally poor in HICs, with annual mortality rates nearing 20-25 percent (van Dijk et al. 2001). Many LMICs report equivalent, if not better, survival on dialysis (Anand, Bitton, and Gaziano 2013). At the same time, several studies have noted poorer provision of long-term care in LMICs: late referral to nephrologists, greater reliance on twice weekly hemodialysis (Bieber et al. 2013), less frequent laboratory draws and use of ancillary medications (Bieber et al. 2013), and lack of enforcement of standards for water treatment for hemodialysis (Braimoh et al. 2012). Patient selection factors may explain this incongruity between better survival despite reported poorer quality of care. In South Africa, where government-sponsored dialysis is offered to patients who fulfill the criteria for eventual transplantation, patients over age 60 years and patients with diabetes are significantly less likely to receive dialysis (Moosa and Kidd 2006). Thus, a rationing process—whether at a societal or familial level—may create artificially better outcomes in LMICs, since a younger, healthier population is most likely able to access expensive dialysis therapy (See chapter 22 in this volume for a more detailed discussion).

Survival on transplantation. Compared to dialysis, first-year post-kidney transplant mortality is less than 10 percent in most HICs (van Dijk et al. 2001). Better survival post-kidney transplant reflects a combination of selection factors—a healthier group of patients receiving transplants and greater efficacy of therapy (Wolfe et al. 1999). Most individuals in HICs receive cadaveric transplants.

In LMICs, reported outcomes for living donor transplantation are similar to those in HICs (Anand, Bitton, and Gaziano 2013). Cadaveric donation is much less common in LMICs due to the lack of deceased donor registries; but in one center's report, it was associated with poorer outcomes than in HICs (Medina-Pestana 2006). Reasons behind the poorer outcomes should be further studied, especially since the recipients tend to have fewer comorbidities and are younger. In most LMICs with flourishing transplant centers—such as Brazil, India, Islamic Republic of Iran, Pakistan, South Africa, and Tunisia—the technical training of surgeons and nephrologists is comparable to that of HICs. However, two factors specific to LMICs may be at play:

- Funding of immunosuppression medication varies; some governments, such as Brazil, pay the full costs; others expect a majority of patients to self-pay. Since immunosuppression medications are expensive, patients may minimize or discontinue their use if asked to self-pay.
- Risks for serious post-transplant infection are likely to be higher in LMICs. An estimated 10 to 15 percent of individuals with kidney transplants develop tuberculosis in endemic regions (Rizvi et

al. 2003, Malhotra 2007). Among those who have a co-infection, the mortality rate has been reported to 75 percent (Chen et al. 2008).

Use of modality. Kidney transplant clearly offers the best survival rates and quality of life for individuals with ESRD. In HICs, kidney transplants meet the need of 30-40 percent of prevalent ESRD patients (Grassmann et al. 2005). Advances in patient selection, organ suitability, and organ availability have increased transplantation rates. National and regional organ donation chains can maximize adequate donor-recipient pairing over a large geographical area to ensure maximal chance of transplantation rate and allograft survival (Gentry, Montgomery, and Segev 2011). Recent changes to the deceased donor system in the United States are anticipated to more efficiently allocate organs.

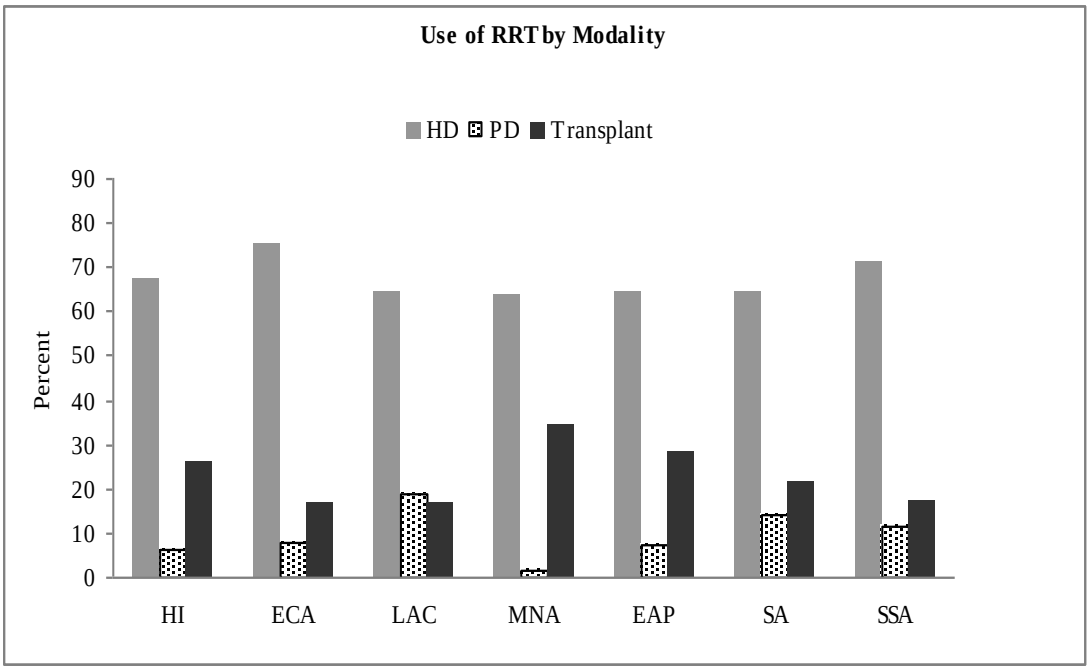
As in HICs, hemodialysis is the most commonly used therapy in LMICs. Transplants are relatively more commonly used in Middle East and North Africa and in South Asia compared with other LMIC regions (figure __.2). In the Islamic Republic of Iran, compensation for donation may drive this trend(Ghods and Savaj 2006). Peritoneal dialysis is relatively more commonly used in Latin America and the Caribbean.

]In addition to organ availability limits, many LMICs struggle with inadequate infrastructure for safe transplantation and post-surgical care (Rizvi et al. 2011). Deceased donor registries do not exist in most countries. Practices such as black market trade and financial compensation are more prevalent and often disproportionally target poorer members of the population as donors (Mendoza 2010).

Figure __.2. Use of RRT by Modality

Note: HD = Hemodialysis; PD = peritoneal dialysis; ECA = Europe and Central Asia; LAC = Latin America and the Caribbean; MENA = Middle East and North Africa; EAP = East Asia and Pacific; SA = South Asia; SSA = Sub-Saharan Africa.

Source: Anand, Bitton and Gaziano 2013.



The preponderance of efficacy data demonstrate equivalent survival for patients on hemodialysis compared with peritoneal dialysis, but hemodialysis predominates as the primary mode of therapy. Approximately 20 percent of patients who receive renal replacement therapy in HICs receive peritoneal dialysis (Anand, Bitton, and Gaziano 2013). Some reasons for this low uptake include skewed provider incentives toward in-center care, lack of patient education about alternate modality, and patient fear of self-care.

Peritoneal dialysis, a relatively low-technology technique that does not require a high-ratio of trained nurses and nephrologists, or specialized facilities with water treatment capabilities, can have greater uptake in LMICs. Mexico and Thailand are exceptions to the generally low use. Historically, Mexican clinicians have been trained in peritoneal dialysis and disseminated the technique (Riella and Locatelli 2007); internists have been able to prescribe peritoneal dialysis (Pecoits-Filho et al. 2007). Following the model of Hong Kong, China, the Ministry of Health in Thailand has tied use of peritoneal dialysis first to reimbursement and supported expansion of peritoneal dialysis (see chapter 22 for a detailed discussion).

Cost and Cost-Effectiveness of Interventions

Screening

The cost-effectiveness of screening for CKD has been extensively studied in HICs. The accuracy of creatinine-based eGFR alone in predicting outcomes and progression has remained questionable; not surprisingly, its use in the general population resulted in incremental cost-effectiveness ratios (ICER) exceeding US$100,000 per quality-adjusted life year (QALY) (Komenda et al. 2014). Narrowing to the diabetic population, however, the ICER for screening was US$23,680 per QALY.

Assessment of proteinuria via urine albumin-to-creatinine ratio is generally considered to be a more reliable test, although Jafar and others (2007) have shown high specificity but moderate sensitivity (46-60 percent) in an Indo-Asian population. The cost of urine albumin-to-creatinine ratio is significantly higher than that of serum creatinine, but more acceptable ICERs were noted for its application to those ages 50 years and older: US$73,000/QALY if performed annually, to $22,000 per QALY if performed every 10 years, compared to no screening (Hoerger et al. 2010). ICERs for individuals with diabetes or

hypertension were US$15,000 per QALY if urine albumin-to-creatinine testing is performed every 10 years.

Targeted screening may be the most cost-effective strategy for HICs, but identifying high-risk individuals in LMICs is difficult, and the cost of and utility loss from the development of ESRD is higher, given the restrictions on renal replacement therapy. Two-stage screening may be a strategy worth investigating (Box __.3). When Howard and others (2010) modeled the use of annual dipstick screening for proteinuria in all Australians ages 50-69 years, followed by confirmatory urine protein-to-creatinine ratio and initiation of treatment, the resulting ICERs were US$5,298 per QALY. Similarly, a study of elderly patients at Veterans Administration hospitals in the United States found that the number needed to treat to prevent a case of ESRD over a three-year period was substantially lower among individuals with dipstick proteinuria, compared with those without proteinuria and modest reductions in eGFR (O'Hare et al. 2014).

Box __.3 Case Study: Integrated Screening Program in Tamil Naidu

A low-cost integrated screening program can be radically effective (Mani 2003, 2005). Working with the Kidney Help Trust of Chennai, Dr. Mani has implemented a program in rural Tamil Naidu in which lay health workers perform a urine test for protein and glucose, and record blood pressure in individuals over age five years (n=25,000). Any abnormalities are further investigated with more specific laboratories after physician evaluation; treatment with low cost drugs is initiated.

The program cost was US$0.27 cents per capita. After two years, compared to an area with similar demographics, the proportion of individuals with eGFR < 80 ml/min/1.73m^2 was significantly lower in the treatment area.

Renal Replacement Therapy Program and Modality Choice

No recent studies from HICs have evaluated the cost-effectiveness of supporting an individual's decision to pursue renal replacement therapy versus palliative care. Most HICs include renal replacement therapy as part of universal-health care packages or government-sponsored insurance programs. In 2011, the U.S. Medicare agency paid US$87,945 per patient for hemodialysis; US$71,630 for peritoneal dialysis; US$99,826 for first year of transplant; and US$12,019 for ongoing post-transplant care (U.S. Renal Data System 2013). Other HICs report similar ranking of costs across modalities.

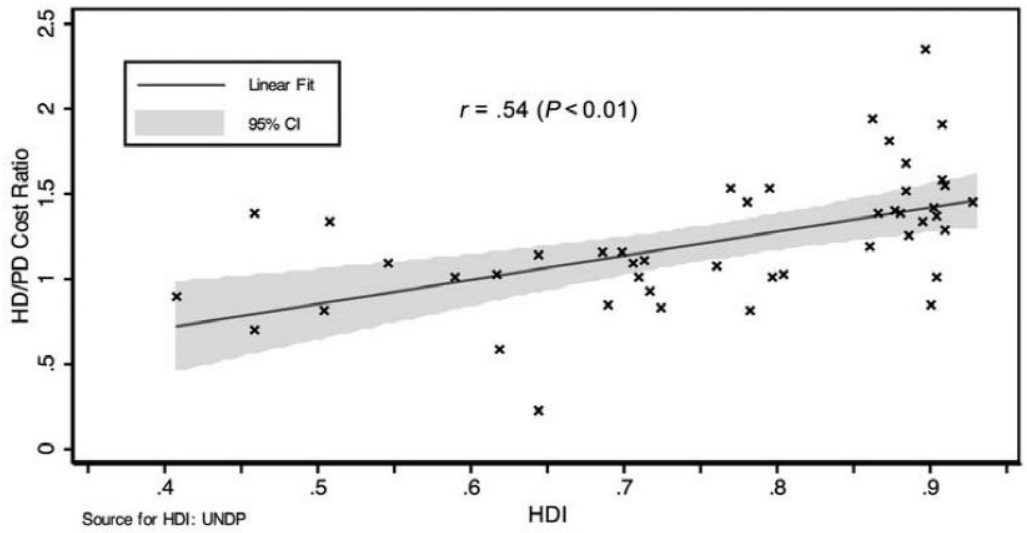
Despite the upfront high procedural costs, transplantation is the most cost-effective form of therapy in the long term due to its efficacy and low maintenance costs (Winkelmayer et al. 2002). Data from LMICs are limited, but these results are likely to be confirmed even in resource-limited settings. However, transplant has several unmodifiable limitations: it can rarely be preemptive; it is contraindicated in patients with serious comorbidity, such as cardiovascular disease, cancer, or infection; most important, it faces a limited supply of organs.

Peritoneal dialysis offers similar survival and quality of life compared with hemodialysis, and based on its cost-rankings in HICs, peritoneal dialysis could be hypothesized to be more cost-effective than hemodialysis (Karopadi et al. 2013). Uptake remains low. Efforts to rein in costs related to ESRD led to the 2011 implementation of bundling rules in the United States, which require packaging several ancillary services into a fixed payment to dialysis facilities. Although the impact of bundling on patient outcomes has yet to be studied in detail, these measures incentivize home-based peritoneal dialysis or hemodialysis. After only two years of implementation, the number of prevalent individuals on peritoneal

dialysis had risen by 30 percent for two of the largest dialysis providers in the United States (Golper 2013).

Despite its lower requirements for specialized treatment facilities and nephrology-trained staff, costs associated with peritoneal dialysis in LMICs are estimated to be equivalent or higher than those of hemodialysis (figure __.3) (Karopadi et al. 2013). Although further study is required to determine the reason for these cost differences, economies of scale and costs of importing peritoneal dialysis solutions and equipment likely play a substantial role. Local manufacturing of peritoneal dialysis solutions and equipment in Mexico and India, for example, has resulted in peritoneal dialysis costs being lower than those of hemodialysis.

Figure __.3. Association of Hemodialysis/Peritoneal Dialysis Cost Ratio, according to the Human Developmental Index



Source: Karopadi and others 2013.
Note: Countries with higher human developmental indexes had cost ratios favoring use of peritoneal dialysis.

Recommendations for Policy Makers in LMICs

While the data on caring for patients with CKD and ESRD in LMICs is limited, some cornerstones of management (e.g., educating primary care physicians to recognize diabetic CKD, or prioritizing kidney transplants in renal replacement therapy programs) will translate directly even in low-resource settings (Table __.5). However others—in particular CKD screening and/or innovative ways of maximizing dialysis provision—require research specific to the LMIC context.

Table __.5 Recommendations for CKD and ESRD care in LMICs

Intervention	Platform	Potential Benefit	Evidence

CKD			
Consider a two-step screening into chronic disease surveillance programs	Government	Identify high-risk individuals for further testing/referral	Limited: Economic modeling based on two observational studies in HICs
Educate physicians about diabetic CKD, the most common form of progressive CKD	Primary care	Prevent ESRD and CV events among patients with diabetes	Strong: RCT evidence from HICs and LMICs
Ensure availability of ACE inhibitors or ARB	Primary care	Delay progression ESRD for a majority of patients with CKD (particularly proteinuric CKD)	Strong: RCT evidence from HICs and LMICs
ESRD			
Develop deceased donor registries	Government	Increase organ availability for kidney transplant, the most efficacious and cost-effective therapy	Strong: Large observational studies and economic modeling from HICs
Create high throughput transplantation centers	Tertiary care	Take advantage of volumes to develop surgical expertise and standardized immunosuppression protocols	Limited: observational studies from one LMICs
If not able to provide transplantation, create relationships with middle-income countries with high throughput transplantation centers	Government	Increase world-wide accessibility for kidney transplant	Expert opinion
Incentivize use of PD	Government	Use economies of scale to decrease costs associated with dialysis provision; create wider access to dialysis using a less-specialized work force	Modest: one meta-analysis and a real life implementation in Thailand
Create palliative care programs for patients unable to sustainably afford dialysis	Government or community level		Expert opinion

Conclusions

Overall, care provision for patients with either AKI or CKD is limited in LMICs, especially since the severe forms of each necessitate use of expensive renal replacement therapy. However several current gaps can be addressed with careful policy consideration.

For AKI, gathering more data on its true incidence and risk factors is crucial. Since the community-based form of AKI may be more prevalent in LMIC, if we can identify the most common etiologies we can work to prevent them. In addition to identifying regional centers that can accommodate patients who acutely require renal replacement therapy, protocols that optimize intensive care at first or second level hospitals are an initial first step in its management. Use of peritoneal dialysis for AKI may be achievable even at second level hospitals but requires further study.

LMICs are likely to face a rising burden of individuals with CKD and ESRD. Current data indicate that screening a high-risk, older population for CKD is cost-effective, but identifying such a population in countries without primary care health care systems is a key challenge. Low-cost strategies, such as the use of a urine dipstick, can be readily integrated into programs for chronic diseases surveillance but also requires further study. Most patients with proteinuric, and to a modest extent, hypertensive CKD benefit from initiation of ACE inhibitor and ARB therapy, which are available as low cost generics.

Finally, although ESRD is rare, large gaps remain between LMICs and HICs in the provision of therapy. Efforts to increase access to renal replacement therapy need to first focus on increasing the provision of transplantation—the most effective and cost-effective form of RRT. Because transplantation is not appropriate for all individuals with ESRD, dialysis is required for any renal replacement therapy program. Peritoneal dialysis—while not clearly more cost-effective in LMICs—holds the most promise in its ability to reach a larger swath of individuals without intensive technical and equipment requirements.

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