Renal involvement in tropical infections

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Renal disease in Tropics: Is it different?

The tropics have unique health care problems that have not been of much concern to rest of the world until recently. Increasing travel and immigration have made neglected tropical diseases relevant for almost all regions in the world. Geographically, the tropical region is limited to an area till 23° 26′ 16″ on either side of equator and characterized by direct overhead presence of sun at least once in a year. This definition encompasses almost one third of earth's landmass, which is home to majority of the world population along with animal and plant biodiversity.[1] Generally, tropics are characterized by a hot climate, usually throughout the year. The level of rainfall varies from as low as 2 cm/year in dry arid deserts to almost 9 m/year in tropical rainforests. Hot and humid climate that is conducive to support life in its various forms is hallmark of tropical ecosystem. Persistence of microorganisms, their reservoirs and vectors is greatly facilitated by this tropical ecology. The great biodiversity adds to complex interactions between them and adds to evolution with changing circumstances. Human contact with this ecosystem in almost unavoidable in most of the poor tropical countries because of prevailing poor social and economic circumstances translating into increased susceptibility to infections and poor access to health care services.

Renal diseases in the tropics aptly reflect the uniqueness of tropical diseases. Acute kidney injury (AKI) in tropics is predominantly community acquired and affects young, previously healthy and economically productive age group.[2]

Infections like malaria, leptospirosis, dengue, scrub typhus and acute gastroenteritis especially in children, toxic envenomations like snake bite or wasp bite, poisonings like copper sulphate, and alternative or over the counter drugs are the main causes for community acquired AKI (CAAKI) in these regions. Though decreasing, obstetric causes like septic abortion or post partum hemorrhages are also important causes of CAAKI. In a recent study from a large tertiary care hospital in South India, AKI was seen in 41.1% of patients with tropical acute febrile illness with the most common causes being scrub typhus, malaria, salmonellosis, dengue and leptospirosis.[3] This is in contrast to developed countries (mostly located in cold temperate zones) where AKI is most often seen in older individuals who have co-morbidities and are admitted in hospitals for various reasons. It is important to note that with fast economic development, increasing life expectancy and high incidence of hypertension and diabetes, this form of hospital acquired AKI is also becoming important in tropical regions. Nevertheless, the burden of CAAKI especially infection related remains huge. Similarly, chronic kidney disease (CKD) in tropics also affects young, is diagnosed late and etiology remains unclear in a 16% patients.[4]

Though infections have been typically considered as a cause of AKI, there is increasing realization that residual damage, which may be subclinical, leads to CKD at least in some of these patients with infection related AKI.[5] Moreover, some infections like malaria,

schistosomiasis, filariasis etc. have been associated with immunologic glomerular injury, which is often resistant to therapy and progresses over time. Therefore, epidemiology of renal disease in tropics is greatly influenced by infections.

Mechanisms of renal involvement in tropical infections

Renal abnormalities in tropical infections range from asymptomatic urinary abnormalities to severe forms of AKI necessitating emergent renal replacement therapy. They can be either related to direct infection of the kidneys and urinary tract or indirect consequence of systemic effects of infection (Table 1, 2). Direct invasion of the tubules in the kidney and resultant tubulointerstitial inflammation leading to AKI has been demonstrated in patients infected with leptospirosis and scrub typhus. Plasmodium falciparum has been shown to affect the glomerular endothelium through cytoadherence of infected red blood cells in circulation. In addition, the kidneys are susceptible to damage by various other mechanisms. Glomerular damage secondary to immune-complex deposition or activation of complement can also occur in some infections e.g. post infectious diffuse proliferative glomerulonephritis seen after streptococcal infections and mesangiocapillary glomerulonephritis seen in quartan malaria and schistosomiasis.

Hemolysis occurring in infections like malaria, scrub typhus or viral infections can lead to hemoglobinuria associated acute tubular necrosis. It is important to note that hemolysis can also be precipitated by some drugs used to treat such infections e.g. quinine and primaquine for malaria in individuals with glucose-6-phosphate dehydrogenase enzyme deficiency, a condition which is especially common in tropical population. Also, antibiotics especially penicillins, cephalosporins and fluoroquinolones used to treat various infections in tropical regions can lead to drug induced allergic tubulointerstitial nephritis. Myoglobinuria secondary to rhabdomyolysis has also been reported as a cause of AKI in infections like leptospirosis and dengue. Patients with tropical acute febrile illnesses are frequently dehydrated at admission. Severe hypovolemia leading to shock is not uncommon in infections leading to acute gastroenteritis especially in children and elderly population, and can lead to acute tubular necrosis. Severe dehydration in children with severe acute gastroenteritis has been associated with renal vascular thrombosis. Kidneys may also be involved due to sepsis related acute tubular necrosis or a thrombotic microangiopathy like state secondary to disseminated intravascular coagulation. Infections e.g. Shigella and Escherichia coli related hemolytic uremic syndrome are also an important cause of AKI in tropics. Rarely, a primary infection like angio-invasive mucormycosis leads to widespread vascular thrombosis and renal infarction. Infections like tuberculosis can lead to scarring and destruction of the collecting system and urinary tract, which may lead to calcification and obstruction. At times, it is diagnosed either incidentally or when patients develop CKD.

Usually, multiple mechanisms are at play in an individual patient and it is difficult to distinguish between different types of infection only on the basis of clinical or biochemical manifestations.

Malaria

Malaria is a protozoal disease caused by microorganism belonging to Plasmodium genus, which is transmitted to humans by bite of Anopheles mosquitoes. With an estimated 207 million cases and 0.63 million deaths in 2012, it is one of most important healthcare problems plaguing the under-developed world.[6] Most of the deaths due to malaria occur in pediatric population in Africa. Renal involvement has been reported with four species namely, Plasmodium falciparum, Plasmodium malariae, Plasmodium vivax and Plasmodium knowlesi.

Renal involvement is in the form of two major clinical syndromes known as acute malarial nephropathy and chronic malarial nephropathy.[7] Though AKI is an uncommon manifestation reported in 3% of cases of malaria, the incidence is particularly high in cases of severe P. falciparum malaria where it can be seen in 60% patients. Acute malarial nephropathy presents as AKI and is most commonly seen in P. falciparum malaria. Parasitization of circulating red blood cells (RBC) by malarial parasite alters morphology and metabolism of RBC and promotes cytoadherence with other RBC, platelets and endothelium, which ultimately lead to microcirculatory failure and organ dysfunction. In addition, immune system activation leading to endothelial injury and immune complex deposition, hemolysis and disseminated intravascular coagulation also play a role in pathogenesis. Though acute tubular necrosis is the most common cause of AKI in malaria, acute tubulointerstitial nephritis, diffuse proliferative glomerulonephritis and mesangioproliferative glomerulonephritis have also been reported. Recently, AKI has also been increasingly reported in association with P. vivax and P. knowlesi malaria.[8,9] Drugs like quinine and primaquine that are used to treat malaria can lead to hemolysis in patients with glucose-6-phosphate dehydrogenase enzyme deficiency. Though renal recovery from AKI seems complete in those who are cured after treatment, data assessing long term renal outcomes is lacking.

Chronic malarial nephropathy, also known as quartan malarial nephropathy is actually a glomerulopathy usually seen in children (4-8 year age group). The presentation is with edema a few weeks after an acute febrile illness due to P. malariae. Investigations reveal nephrotic range proteinuria and severe hypoalbuminemia. This condition does not respond to antimalarial therapy or immunosuppressive therapy with steroids. Its course is later marked by appearance of hypertension and renal failure.

Leptospirosis

Spirochete organism belonging to the genus Leptospira causes leptospirosis, one of the most important zoonoses in the world. Though rodents like rats are considered the most important disease reservoir hosts, this organism is seen in a wide range of mammals including the common domesticated animals like cattle, sheep, pigs and dogs. The organism is acquired through contact of abraded skin or mucous membranes in humans with infected urine or tissue of host. Disease transmission is seen during or after rainy season and flooding, and it is an occupational hazard in endemic regions. The incidence is approximately 100 times more in humid tropics as compared to temperate regions. During epidemics and in predisposed population, a high incidence of 100 cases per 100000 population may be seen.[10]

AKI is a common manifestation in leptospirosis seen in 40-60% patients.[11] Direct infection of the kidneys leading to tubulointerstitial nephritis is the predominant mechanism of renal involvement. AKI is usually non-oliguric and occurs during the second or immune phase of infection and may be associated with hepatic and pulmonary involvement. Also, tubular defects especially the involvement of proximal convoluted tubule lead to hypokalemia which is an early and common manifestation.[11] Though prompt recovery of renal function is seen in patients who respond to treatment, urinary concentrating defects may be present at 6 months after apparent recovery when they are meticulously looked for.[12]

Dengue

World Health Organization (WHO) identifies dengue as the most rapidly spreading mosquito borne disease in the world which is quickly crossing regional borders.[13] With a 30-fold increase in incidence over past 50 years, it is an emerging pandemic prone viral disease. The South East Asia and Western Pacific regions in tropics bear about 70% of the total global burden of this disease. It is caused by dengue virus which is a Flavivirus transmitted by bite of Aedes aegypti mosquito. The clinical spectrum ranges from acute febrile illness with myalgias to presence of hemorrhagic manifestations and shock in its severe form. As there are no specific drugs available, prompt identification of complications and supportive therapy are the mainstay of management.

AKI is a known complication in patients infected with dengue. Though figures vary according to different definitions used in different time periods, a large study from Taiwan reported symptomatic renal failure in up to 4% of patients with dengue infection.[14] A recent study from India reported AKI in 10.8% of patients with dengue infection.[15] Shock secondary to hemorrhage or dengue shock syndrome, and rhadbomyolysis leading to acute tubular necrosis are main causes of AKI. Direct involvement of the kidneys leading to renal failure has also been suggested in patients who develop renal failure without associated shock or rhabdomyolysis.[16] Renal involvement is more commonly seen in dengue hemorrhagic fever and dengue shock syndrome, and is an independent predictor of mortality.[14,15,17]

Scrub typhus

Scrub typhus is a zoonosis caused by bacterium Orientia tsutsugamushi, which is transmitted to humans by the bite of larvae of trombiculid mite. This disease, which is mostly seen during and after the rainy season, mainly affects people who work outside and are exposed to shrubs and vegetation, on which the vector thrives. The recent increase in reports of scrub typhus cases from the Indian Subcontinent highlight the changing epidemiology of this disease.[18] Though it is likely that a part of it may be related to improved diagnostic techniques that were not previously available in these regions, but reports from urban regions and finding of new vector underscore the importance of evolution of disease transmission and need of studying it.[19]

Until recently, renal involvement in scrub typhus has been considered an uncommon manifestation that was mainly attributed to widespread hemodynamic alterations occurring in severe infection. However, the most recent data especially from the Indian Subcontinent have shown that AKI, as it is defined today, may be seen in 30-60% of patients treated at tertiary care referral centers.[18] If we take into account asymptomatic urinary abnormalities, renal abnormalities can be seen in up to 80% patients.[18] Injury to vascular endothelium, tubules and interstitial inflammation are main mechanisms of renal involvement. Presence of an eschar is an important clinical clue but may be missed in dark skinned individuals or if it is not meticulously looked for. It is important to remember that the organism is resistant to commonly used antibiotics like penicillins, aminoglycosides and fluoroquinolones. The two most commonly used drugs to treat this disease are doxycycline and azithromycin. Therefore, in areas of high endemicity, doxycycline is frequently used as an empirical therapy to cover for scrub typhus. Though AKI has been shown to be a predictor of mortality in these patients, it is still not clear as to what is the actual clinical significance of other renal abnormalities.

Others

Schistosomiasis caused by Schistosoma, a trematode, is another important tropical parasitic infection that can involve the kidneys or urinary tract. S. mansoni, which is endemic in South America and Africa, can lead to immune complex glomerulonephritis, also known as schistosomal nephropathy, that produces a nephrotic syndrome like state.[20] It is poorly responsive to anti-microbial or immunosuppressant drug therapy, and progresses to renal failure with time. S. hematobium is found in Africa and Middle East, and leads to inflammation and later fibrosis and scarring of the lower urinary tract. It can present with hematuria and obstructive symptoms of the urinary tract

Immune complex mediated glomerulonephritis has been described in lymphatic filariasis caused by nematodes Wuchereria bancrofti, and Brugia malayi.[20] Like chronic malarial nephropathy, response to antimicrobials or immunosuppressants is unsatisfactory. Chyluria is an uncommon complication seen in filariasis where patient presents with intermittent milk like white urine. Rupture and drainage of dilated and scarred lymphatic channels into the urinary tract is responsible for it. Just antimicrobial therapy may not suffice and sclerotherapy of dilated channels with povidone iodine or silver nitrate is required in most cases.

Salmonellosis, caused by bacteria of the genus Salmonella, is a common infection seen in tropics due to poor hygiene and sanitation. Though AKI is a rare manifestation, the absolute number of cases with AKI may be high as there is huge burden of this disease.[3] Similarly, acute diarrheal diseases like cholera or other bacterial or viral gastroenteritis can lead to AKI due to severe shock. Rarely, renal arterial thrombosis in patients with such severe shock has been described especially in children. Mycobacterial diseases like tuberculosis and leprosy can also lead to renal involvement. Tuberculosis is characterized by involvement of the collecting system and urinary bladder, which may go unnoticed during the acute phase. It leads to scarring, stricture formation and calcification of the urinary tract and occasionally kidneys. Granulomatous interstitial nephritis, which presents as rapidly progressive renal

failure, is another important manifestation of renal tuberculosis. Secondary amyloidosis with renal involvement, presenting as nephrotic syndrome, is an important late complication seen in tuberculosis. Leprosy, another mycobacterial disease prevalent in tropics, can also lead to secondary amyloidosis. It can also cause immune complex glomerulonephritis especially in multi-bacillary and erythema nodosum leprosum forms. Various viral infections like hepatitis B, hepatitis C, human immunodeficiency virus and viral hemorrhagic fevers e.g. hantavirus can also have a wide variety of renal involvement.

Clinical approach and management

Tropical infections commonly present as acute febrile illness with varying degrees of multisystem involvement, renal involvement being one of them. A definite diagnosis is obtained either by demonstration of microorganism in culture or in peripheral blood film as in case of malaria or its genetic material in biological samples by nucleic acid testing or four fold rise in specific antibody titers in convalescent serum samples. Usually, patients are investigated for all the possible etiologies prevalent in that area depending on available resources. Unfortunately, the poor tropical countries lack even basic healthcare delivery infrastructure at most of the places. Though rapid bedside serologic tests are available for some of these infections, they should be interpreted with caution in the absence of robust local seroprevalence and serological titers cut off data for acute infections. As these diseases are endemic and serological response may be delayed, there is a likelihood that such measurements may lead to fallacious conclusions especially when a single time antibody titer cut off is used. The diagnoses in most of the cases are presumptive and hence, initial treatment is largely empirical based on local experience and epidemiology. Nevertheless, a syndromic approach based on predominant clinical manifestations has been proposed as a guide to initiate treatment till a definite diagnosis is made.[21] It is important to note that experts have repeatedly emphasized that it is just a guide and does not replace continuous monitoring, evaluation and clinical judgement.

It is not unusual to find patients with non-infectious renal diseases who actually come to medical attention because their basic renal disease has been either precipitated or aggravated by a tropical infection. Small vessel vasculitis, anti glomerular basement membrane disease and thrombotic thrombocytopenic purpura or atypical hemolytic uremic syndrome are some of the diseases occasionally diagnosed in such patients who initially seem to be suffering from a typical tropical acute febrile illness but later have an atypical course or fail to recover. Therefore, a high index of suspicion is always required. A renal biopsy is preferable whenever the diagnosis is in doubt and alternative diagnoses have important therapeutic implications e.g. need of starting immunosuppression or plasmapheresis. The increasing incidence of diabetes and hypertension, two most common causes of CKD, in tropical countries is translating into a large number of patients with pre-existing CKD who develop superimposed AKI due to tropical infections. At times, patients may be co-infected with multiple microorganisms as all infections share the common ecosystem, and it may further complicate the clinical presentation and response to therapy.

The treatment has two major components namely, supportive therapy to ensure hydration, maintain oxygenation, relief from symptoms like fever or bodyaches, manage electrolyte abnormalities and provide dialysis as and when required; and specific antimicrobial therapy directed against underlying cause. Avoiding drug induced renal injury is an important concern while managing patients with renal involvement. Local resources guide the choice of renal replacement therapy. Both hemodialysis and peritoneal dialysis are used for patients requiring dialysis. In fact, peritoneal dialysis can be life saving in resource-constrained settings, as it requires little expertise and minimal infrastructure. It is preferable that patients with suspected or proven renal dysfunction are referred to tertiary care referral centers which can provide dialytic support if required. Usually, empirical therapy with a combination of two or more drugs like artesunate, ceftriaxone and doxycycline is started immediately in these patients and further tailored according to investigation results. The management of chronic complications like nephrotic syndrome and chronic kidney disease is largely supportive after eradication of any ongoing active infection.

Symptomatic renal involvement in tropical infectious diseases signifies major organ dysfunction and is usually an indirect reflection of severity of disease. Once appropriate specific antimicrobial therapy has been initiated, the focus is on prevention, timely identification and management of complications arising out of major organ dysfunction. In this regard, monitoring for development of AKI, control of reversible or preventable risk factors like dehydration, and timely initiation of dialysis once AKI becomes established are very important. Though lack of resources and infrastructure hinder prevention, control and management of tropical infectious diseases, a lot of progress has been made and incidence of most of these diseases is coming down. However, certain diseases like scrub typhus are re-emerging. Increase in population at risk due to rapid population growth, deforestation, industrial development, frequent travel and appearance of lifestyle related diseases are changing the epidemiology of tropical infections. Unfortunately, long-term disease registries that continuously collect patient data are almost non-existent in tropical countries. Creating disease registry will help re-define the epidemiology with changing times, identify lacunae in current understanding, generate questions, validate newer and simple diagnostic tests, identify targets for intervention, and finally assess the impact of interventions for achieving the goals of public health.

Table 1: Mechanisms of renal involvement in tropical infections

Direct involvement of kidneys or urinary tract by micro-organisms	
1	Tubulointerstitial toxicity
2	Injury to glomerular endothelium
3	Injury to the collecting system and urinary tract
Indirect involvement secondary to systemic effects of infection	
1	Hemolysis
2	Rhabdomyolysis
3	Hypovolemic shock
4	Septic shock
5	Microvascular injury in disseminated intravascular coagulation
6	Immune complex deposition in glomeruli
Drugs used to treat infections	
1	Hemolysis
2	Allergic tubulointerstitial nephritis

Table 2: Morphologic forms of renal injury related to tropical infections*

Glomerular	
1	Immune complex glomerulonephritis
2	Thrombotic microangiopathy
3	Secondary amyloidosis
Tubulointerstitial	
1	Acute tubular necrosis
2	Acute tubulointerstitial nephritis
3	Granulomatous interstitial nephritis
Vascular	
1	Vascular thrombosis (e.g. acute gastroenteritis in children, angio-invasive mucormycosis) leading to renal infarction
2	Thrombotic microangiopathy
Acute cortical necrosis	

*These are not mutually exclusive. Mostly a combination of these with one predominant form would be found in an individual patient.

References

1. *State of the Tropics 2014 Report. Townsville: James Cook University; 2014.*
2. *Jha V, Parameswaran S. Community-acquired acute kidney injury in tropical countries. Nature reviews Nephrology 2013;9:278-90.*
3. *Basu G, Chrispal A, Boorugu H, et al. Acute kidney injury in tropical acute febrile illness in a tertiary care centre—RIFLE criteria validation. Nephrology Dialysis Transplantation 2011;26:524-31.*
4. *Rajapurkar MM, John GT, Kirpalani AL, et al. What do we know about chronic kidney disease in India: first report of the Indian CKD registry. BMC nephrology 2012;13:10.*
5. *Leung KC, Tonelli M, James MT. Chronic kidney disease following acute kidney injury-risk and outcomes. Nature reviews Nephrology 2013;9:77-85.*
6. *World Malaria Report 2013. World Health Organization; 2013.*
7. *Barsoum RS. Malarial Acute Renal Failure. Journal of the American Society of Nephrology 2000;11:2147-54.*
8. *Kaushik R, Kaushik RM, Kakkar R, Sharma A, Chandra H. Plasmodium vivax malaria complicated by acute kidney injury: experience at a referral hospital in Uttarakhand, India. Transactions of The Royal Society of Tropical Medicine and Hygiene 2013;107:188-94.*
9. *William T, Menon J, Rajahram G, et al. Severe Plasmodium knowlesi malaria in a tertiary care hospital, Sabah, Malaysia. Emerging infectious diseases 2011;17:1248-55.*
10. *Human leptospirosis : guidance for diagnosis, surveillance and control. World Health Organization 2003.*
11. *Andrade L, de Francesco Daher E, Seguro AC. Leptospiral Nephropathy. Seminars in Nephrology 2008;28:383-94.*
12. *Daher Ede F, Zanetta DM, Abdulkader RC. Pattern of renal function recovery after leptospirosis acute renal failure. Nephron Clin Pract 2004;98:c8-14.*
13. *Dengue guidelines, for diagnosis, treatment, prevention and control. World Health Organization; 2009.*
14. *Kuo M-C, Lu P-L, Chang J-M, et al. Impact of Renal Failure on the Outcome of Dengue Viral Infection. Clinical Journal of the American Society of Nephrology 2008;3:1350-6.*
15. *Mehra N, Patel A, Abraham G, Reddy YNV, Reddy YNV. Acute kidney injury in dengue fever using Acute Kidney Injury Network criteria: incidence and risk factors. Tropical Doctor 2012;42:160-2.*
16. *Lima EQ, Gorayeb FS, Zanon JR, Nogueira ML, Ramalho HJ, Burdmann EA. Dengue haemorrhagic fever-induced acute kidney injury without hypotension, haemolysis or rhabdomyolysis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2007;22:3322-6.*
17. *Khalil MA, Tan J, Awan S, Rangasami M. Predictors of hospital stay and mortality in dengue virus infection-experience from Aga Khan University Hospital Pakistan. BMC Res Notes 2014;7:473.*
18. *Kumar V, Kumar V, Yadav AK, et al. Scrub Typhus Is an Under-recognized Cause of Acute Febrile Illness with Acute Kidney Injury in India. PLoS Negl Trop Dis 2014;8:e2605.*

19. *Tilak R, Kunwar R, Wankhade UB, Tilak VW. Emergence of Schoengastiella ligula as the vector of scrub typhus outbreak in Darjeeling: has Leptotrombidium deliense been replaced? Indian journal of public health 2011;55:92-9.*

20. *Barsoum RS. Parasitic kidney disease: milestones in the evolution of our knowledge. American journal of kidney diseases : the official journal of the National Kidney Foundation 2013;61:501-13.*

21. *Singhi S, Chaudhary D, Varghese G, et al. Tropical fevers: Management guidelines. Indian Journal of Critical Care Medicine 2014;18:62-9.*