Review Articles

Renal failure in the tropics

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Journal of the Ceylon College of Physicians, 2002, **35**, 47-53

The study of nephrology began with the original morphological descriptions of the kidney by Marcello Malphigni in Padua in the 17th century. Subsequently Richard Bright in 1827 with his description of Nephritis ensured for himself an exalted place in the annals of medical history[1]. The last 5 decades saw the greatest advances in renal medicine with nephrology recognised as an important speciality. The increasing interest in renal disease led to the 1st World Congress in Nephrology being held in Geneva in 1960 and thereafter regular Congresses have been held across the globe. At these parleys the different branches of clinical nephrology, which included Tropical Nephrology, were discussed which resulted in the formation of the Asian Colloquium in Nephrology and later the Asian Pacific Society in Nephrology. During the last 25 years many meetings have been held by these two bodies to discuss and resolve renal problems pertaining to the tropics.

The tropics constitute all countries lying between the Tropic of Cancer and the Tropic of Capricorn. This band across the globe includes much of South America, Africa, certain countries in the Middle East, South East Asia, the Far East and the Northern Territories of Australia.

An essential question that has to be addressed is, what are the factors which are of vital importance in the pathogenesis and treatment of renal failure in the tropics[2]:

1. Physical environment and demography
2. Biological endowment
3. Social environment
4. Health care system
5. Productivity and wealth of the countries concerned

The first includes climate, zoonosis, World travel, human reservoirs and hospital acquired diseases.

Productivity and wealth of nations are macro-economic factors determining all aspects of health problems in each country[3]. They could be assessed by the Gross National Product (GNP) and the per capita income of the respective countries. It is a well known fact that the per capita incomes of the developed nations are strikingly higher than most of the developing countries. They belong to the higher income groups as classified in the World Development Report of 1998/1999, ie over US $20,000. In contrast, most of the developing countries in the tropics belong to the middle and lower income groups. The per capita income of Latin American nations vary between 950 and 4720 US dollars, the highest being Brazil, while the Asian countries have a lower GNP apart from Singapore and Hong Kong. The middle Eastern countries including Saudi Arabia come within the middle income range, while the African territories within the tropics belong to the lower income groups. To some extent the GNP determines the money available to be spent on health programmes which may range from 1% in the tropics to 9-10% in the developed countries[4]. Having dwelt on the various economic factors as a prelude to this review it is necersary to describe and discuss problems concerning renal failure in the tropics.

Renal failure is classified as 1. Acute Renal Failure (ARF) where there is a sudden deterioration is renal function which could be reversible or in some instances irreversible and 2. Chronic Renal Failure (CRF) which is caused by progressive renal disease ending in End Stage Renal Failure (ESRF). The health determinants discussed earlier greatly influence:

1. The diverse aetiology spectrum of ARF
2. The preventive aspects of ARF
3. The problems concerning renal replacement therapy of ARF
4. The causes and prevalence of renal disorders leading to end stage renal failure (ESRF), to a lesser extent and
5. Most importantly, the treatment and management of patients with ESRF – the organisation of dialysis and transplant programmes. ARF is customarily divided as pre-renal, intra-renal or intrinsic renal disease and post renal types. Although this is a

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good clinical working classification ARF constitutes a more detailed entity as recent work at the sub-clinical level indicates its pathogenesis, at the cellular level.

Recent work on pre-renal ARF and ATN has indicated a stage of pre-renal failure caused by increased glomerular vascular resistance, the unique glomerular micro-circulation with intrinsic modulation of filtration and altered tubulo-glomerular feedback[5]. At this stage there are no renal structural changes, but in the presence of adverse events, adverse interventions and drugs, there could be a breakdown in these mechanisms leading to pre-renal failure with structural changes, intra renal disease, causing oligo-anuric ARF. Furthermore, ATN sometimes also called vaso-motor nephropathy can be A. Ischaemic, B. Toxic, C. or both. In the former ischaemia with loss of microvilli and marker enzymes leads to revascularisation with lethal necrosis and more damage. The ultimate stage is one of repair. The stage of revascularisation could be a more dangerous phase with the effects of monocyte/macropharge cytokines – interleukins 1-6, tumour necrosis factor a and b, neutrophil sequestration and oxygen free radicals from zanthines. Furthermore, myoglobin, uric acid, iron, calcium, altered enzymes, endothelial injury, complement activation, cell acidosis and importantly endo-toxins from the gut has its adverse effects. Knowledge of these intrinsic mechanisms of ARF will enable practising physicians in the tropics to adequately manage the earlier phases in ARF[6].

Other clinical classifications for ARF are – the aetio pathogenic classifications[7].

1. Ischemic ATN
   Hypotension
   Septic shock
   Traumatic shock crushed limb, major surgery, obstetric

2. Decreased Intravascular Volume
   Congestive heart failure, cirrhosis, nephrosis, peritonitis

3. Disease of Small Arterioles
   Glomerulonephritis (5%) often with vasculitis; hemolytic-uraemic syndrome

4. Tubulo-interstitial Disease
   Allergic (NSAIDS, Contrimoxazole, Ciprofloxacin)
   Infections, Hanta Virus, leptospirosis

5. Tubular/obstructive ARF
   Nephrotoxins eg Radio-contrast agents.
   ACE inhibitors, NSAIDS, Aminoglycosides, amphotericin B, Cisplatatinum.
   Myeloma Casts
   Uric acid overproduction (tumour lysis syndrome)
   Rhabdomyolysis
   G6PD haemolysis with hypovolemia, malaria
   Hepato-renal syndrome

6. Occlusion of Large Renal Arteries
   Operative arterial clamping more than 30 minutes
   Atheromal renal artery stenosis/thrombosis
   Cholesterol embolism

This classification leads to considering the occurrence of ARF under 3 categories[8]:

1. Medical causes
2. Surgical causes
3. Pregnancy related ARF

While the pregnancy related ARF is declining in most of the tropical countries to 5% or less, it is still appreciable in certain parts of Africa at 15%, while in contrast, surgical causes are on the rise.

Lastly a further heading under which ARF could be discussed is

a. Hospital acquired ARF
b. Community acquired ARF – mainly due to environmental factors

Hospital acquired ARF is considered to be the prime cause of ARF in the high income group of the developed nations and in the tropical regions of Singapore and Hong Kong.

However, today it is becoming increasingly important as a cause in the middle and lower income groups in tropical countries. This category includes[9]:

1. Surgery – Hepato Biliary Surgery, Cardiac Surgery, Neurosurgery, Vascular and Abdominal Aortic Surgery
2. Trauma associated with wars and natural disasters
3. CCF
4. Transplant ARF – renal hepatic and cardiac
5. Hepato-renal failure – MOF
6. Burns
7. Post myocardial infarction
8. Use of contrast media in modern radiology
9. Sepsis and septicaemia

Thus this list contrasts somewhat with Community Acquired ARF which is unique and virtually confined to the tropics and makes the study of ARF in the tropics a fascinating subject[10,11,12,13,14,15,16].

In all these types of ARF, the more seriously ill patients fall into the category of the acutely ill or critically ill ARF with a high Apache 11 score > 20 needing ICU treatment which should be available in all major hospitals and even in many suburban hospitals in the tropics.

The critically ill is a serious problem in the tropics unless facilities are forthcoming for total parental alimentation and Renal Replacement Therapy (RRT) which needs to be instituted. It causes a high mortality due to respiratory failure and assisted ventilation, DIC, MOF Rhabdomyolysis, prolonged oliguria, poor tolerance to RRT and cardiac instability episode, hypotension and cardiac arrhythmias. There is also a need to consider sepsis and septicaemia causing endotoxaemia which have an important place in tropical renal failure. It occurs in both HARF and Community Acquired ARF. The various organisms causing endotoxaemia are the Stapholococcus, Pseudomonas, Sp, E.coli, Candida and Aspergilosis, endotoxins reduces renal blood flow and causes ARF due to variety of mechanisms. Acting through sympathetic nervous system, formation of Angiotensin 11, production of Thromboxanes, Endothelin, IV coagulation endotheliai damage and adherence of leucocytes to vascular endothelium.

The important causes of ARF in a country-wise fashion within the tropics need consideration.

The Latin American States have a relatively high incidence and have progressed much over the last 50 years to design a health care system in keeping with the elevation of its social schemes. Due to their steady economic growth, in spite of its environmental problems, they aim to achieve the standards of the developed nations. However Community ARF still prevails while Hospital acquired ARF is on the rise. There is a common occurrence of Infections, Dengue haemorrhagic fever, gastro-intestinal disease, snake bite due to C.D. terrificus (rattlesnake) and Bothrops species[17].

The African territories are burdened with its environmental and economic problems, low GNP and the heterogenicity of its population[18]. Hence it has an unique spectrum of ARF varying across the different states. Pregnancy related ARF is high due to abortions. Other causes are hypertension and aorto-arteritis, viral haemorrhage fevers – Congo fever, arbo virus, lassa, marburg and Ebola viruses. Snake bite, infections, G6PD – malaria, calculi, AIDS and hepatitis B, herbal and plant toxins, schistosomiasis and poisons due to hair dye, copper sulphate and Kalazar.

In the Middle eastern countries like Saudi Arabia and Yemen, Hospital acquired ARF is on the increase, other causes being G6PD malaria, calculus disease, sistoma and snake bite[19].

Common to all South East Asian countries are gastrointestinal infections, epidemics of cholera, typhoid, malaria and G6PD, Sepsis and Hospital acquired ARF occur. In Pakistan – in addition stone disease occurs[20].

Bangladesh has its spectrum of ARF common in all other South East Asian countries[21]. In the north of India there is an increase in Hospital acquired ARF and in addition to the common causes prevalent in the countries of South East Asia there exists stone disease, copper sulphate poisoning and mercuric hydrochloride poisoning. In contrast the common causes found in South India also include snake bite and leptospirosis[24,25].

In Myanmar (Burma) snake bite and leptospirosis are the common causes, while in Thailand snake bite, leptospirosis and plant poisons take their toll[24,25].

Snake bite and Dienkol bean poisoning occur in Malaysia and in Indonesia snake bite is an important cause.

Lastly, Taiwan has its quota of snake bite, leptospira and raw carp bile poisoning, while in South China herbal toxins and Hantana virus infections are the main causes.

The Sri Lankan experience. In an analysis of 448 cases having ARF, medical causes were 82% with a mortality of 16%. Snake bite was a common cause with 44% and 10% mortality. Infections were 33% with 12% mortality. They were leptospirosis (18%) and malaria with or without G6PD deficiency (4%). Paraquat was the cause in 4% and glomerulonephritis in another 6%. The surgical causes were 13% with a mortality of 28% while the obstetric causes were 6% with a mortality of 10%[26].

In Sri Lanka too there is a rising incidence in Hospital Acquired ARF as in other parts of the tropics. Of the 448 patients there were 50 (11 %) with a mortality of only 12%. The medical causes were 40% being gastroenteritis, sepsis, drug induced and transfusional. The surgical causes were 40% and the pregnancy group 20% due to haemorrhage. It differs from

the general case mix of Medical 82%, Surgical 13% and Obstetric 5%. The mortality in the 3 groups was Medical 15%, Surgical 15% and Pregnancy nil. Briefly some of the causes of ARF in the tropics will be considered.

Snake bite – Man has to live with the Serpent, it stabilises the ecology and at the same time causes tragedy. The snakes causing ARF are the Russells viper, Saw scale viper, Hump nosed viper, Pit viper, Sri Lankan cobra, the Rattle snake, C D Terrificus, Botrop species, some Australian terrestrial snakes and Sea snakes, all causing Rhabdomyolysis[27].

The renal effects depend on the quantum and composition of the venom, the main components being proteastas phospholipidase A2, various enzymes and other nephrotoxic substances[28,29,30]. The distribution of Russells viper in the tropics is wide spread, of Echis earinatus and Pit vipers and the Australian terresstrial snakes together with the snakes of Sri Lanka have a wide spectrum. Interestingly CRF could rarely occur following the acute phase. Histologically glomerular and tubular changes occur – glomerulitis and tubular interstiatial disease and even cortical necrosis.

Leptospirosis – Leptospirosis in Sri Lanka is due to L. interogans – serotype icterohaemorrhagiae, pyrogenese, javanica and ceylonicus. The former is the more serious type with multiple organ failure. In Thailand and Singapore the organism is L. batavia, while in South India it is L. interogans with sub-groups similar to that in Sri Lanka and in Taiwan it is L. australis[31,32].

Malaria – Malaria occurs in its most severe form with falciparum infections. It has a widespread distribution with a possibility of being imported to the developed countries due to air travel, Non immune visitors to endemic areas in the tropics are more likely to develop severe infection and renal failure than local residents[33,34].

Virus infections – Viruses like the Hantana, Aids and Hepatitis B are emerging as important causes of renal failure in the tropics and more recently renal mycoses and invasive fungal infections which are usually opportunistic pathogens are of interest – namely, Aspergilosis, Mucor, Cryptococcus, Histoplasma and Candida[35].

Since ARF in the tropics is to a great extent influenced by health programmes and financial constraints, the prevention of the illness is of paramount importance.

Prevention of ARF – This would involve well documented modes of treatment like optimum volume status and circulation, avoidance of contrast-induced nephropathy with hydration, attention to rhabdomyolysis and haemolysis, the rational use of drugs like mannitol, loop diuretics, dopamine, calcium channel blockers, in addition to alkalinisation of urine and the prudent use of commonly used nephrotoxic drugs[37]. The adequate treatment of sepsis need not be over emphasised in the tropics. Future development in treatment in ARF. Blocking the over production of endothelin, the prevention of clustering of tubular cells which could be prevented by monoclonal intercellular adhesion molecules (ICAM - 1) and by the arginine-glycine-aspartic acid (RGD) peptides.

The potential role for the administration of growth factors like IGF-1 and scavengers of reactive oxygen species are also being experimented upon and relevant to the tropical ARF.

Renal support – The initial supportive measures of peritoneal dialysis and haemodialysis which may suffice for the haemodynamically stable patient has been modified by the continous renal replacement therapies in critical care nephrology thereby regulating azotemia, fluid, acid base and electrolyte status[38]. These treatment modalities include continuous peritoneal dialysis with automated cyclical regimes, continuous arteriovenous haemofiltration (CAVH), together with dialysis (CAVHD) and pump incorporated venovenous haemofiltration (CVVH or CVVHD). Slow continuous ultrafiltration (SCUF) is also being used. Attention is also being paid to the porosity of membranes in continuous renal replacement therapy such as AN69. These later methods are relevant to the affluent renal centers in the tropics[39].

Mortality trends – With renal replacement therapy patients die with ARF rather than from ARF. The mortality has not reduced appreciably over the last twenty years in many countries[40,41]. Lower mortality is observed with early transfer to major units, ATN and obstructive uropathies, non-oliguric ARF and obstetric ARF. Relative factors are age over 45 years, associate disease, early diagnosis and treatment policies. Serious complications increase the mortality, namely MOF and jaundice, mechanical ventilation, septic shock syndrome, persistent hypotension, GI bleeds and intravascular haemolysis or coagulation defects.

The exact mortality varies with the case – mix in different countries of the tropics and could range from 10% to as high as 40-60% especially in critically ill cases with MOF.

In striking contrast to the wide ranging aetiology of acute renal failure in the tropics, chronic renal failure (CRF) has an aetiological spectrum which is fairly narrow in all countries concerned, the only difference being the incidence and a few diseases peculiar to certain locations. In the main the aetiological spectrum is even similar to that in developed nations. Hence in the health determinants of disease physical environment and demography have less importance. In the USA diabetes accounts for 37%, hypertension 30% and glomerular nephritis 12% of all cases. A similar spectrum is seen in the Latin American States. In Saudi Arabia diabetes is the cause in 30% and stone disease in 14%, while in African countries chronic pyelonephritis and Bilharzia are prominent causes. In North India diabetes accounts for only 14% when compared to South India where it is 30% and glomerular nephrilis is between 11% and 17%[42,43].

In Sri Lanka in a study of 336 patients chronic glomerular nephritis was 22%, chronic non-obstructive pyeilonephritis was 14%, and diabetes 12%. It is of some interest to note that in all tropical countries there is a small proportion of patients with heredofamilial diseases like adult polycystic disease, Alports disease, myeloma, and malignancies. In addition aortoarteritis with hypertension occurs in Africa, Singapore and India. Amyloid disease is found in North India, Saudi Arabia and stone disease in parts of India and Pakistan. IgA nephropathy, of much interest in recent times, has a significant incidence in India, Singapore, Malaysia and Yemen in the Middle East. In Sri Lanka snake bite is also a cause[44,45].

Having considered the aetological factors in CRF, some general facts regarding CRF in the tropics need mention. The benefits of RRT for ESRF are firmly established[46]. However the availability is still limited in the developing countries which includes the tropics. The general problem of providing health care in these tropical countries is likely to increase with adverse demography and possibly diminishing resources. The ESRF programme seems unbalanced even in the UK, while the transplants performed and results obtained compare well with any country due to organ sharing, the demand for sufficient dialysis facilities, particularly haemodialysis (HD) remains largely unmet. (Report of the Renal Association of the UK 1995). The reported incidence of ESRF in the third world may vary from 40 – 240 per million population. The Latin American states[47], and the Middle East have fared better regarding RRT due to organised programmes with cadaver organ sharing, than Asian, Far Eastern and African countries where there is inadequate government organised programmes for treatment which has to be on an individual basis sponsored by benefactors and private organisations. This is also a very noticeable feature with respect to CAPD and Haemodialysis again inadequate in these countries.

Successful renal transplant is the only hope for long term survival for most patients[48]. It is estimated that about 3% to 10% of ESRF patients in the developing nations of the tropics are able to procure transplants using invariably live donors. The problems concerning cadaver organ sharing and brain death are being looked into in several of these countries including Sri Lanka[49], a step in the right direction. However, the position in the tropics is not altogether hopeless inspite of multiple constraints as transplants were done as early as 1972 in India and later 1975 in Malaysia and in 1979 in Saudi Arabia.

Latin America has done over 20,000 transplants while in India there have been over 2,500 and lesser numbers in the other South East Asian countries[50]. Over the last decade there has been a constant and appreciable increase in transplants performed in all these countries. In India it is estimated that about 4400 renal transplants are done annually. This has led to commercial trafficking in human organs in India and certain other Asian countries causing life threatening infections like HIV and Hepatitis B from paid donors. In recent years legislation has been introduced to stop this trend. Even Sudan in Africa, one of the least developed nations in the tropics, have done reasonably well in the field of transplantation. The first kidney transplant in Sri Lanka was done in 1981[48] and since then several hundreds have been done. Problems concerning RRT were discussed recently at the first International Congress on Transplantation in developing countries held in Singapore. The need for an ESRF register was stressed for planned management. The tasks lying ahead into the next millenium are phenominal but not impossible to achieve as all RRT programmes are heavily dependent on the country's productivity and wealth. Hence all important in the tropics is the need for:

1. Prevention and adequate management of renal disease giving rise to CRF
2. Prevention of progression of renal failure once it occurs[51,52].

Prevention requires proper management of primary renal diseases like glomerular nephritis, renal infections, reflux nephropathy, hypertension and adequate control of diabetes. Regarding the prevention of progression, the control of hypertension and infections are of prime importance as in proper drug prescribing and control of hypertension. Much experimental work has been done on dietary interventions. Low protein diets, phosphate restriction and supplement with fish oil have led to controversy and produced conflicting results. At present, reduction in the dietary protein may only be useful between a fall in glomerular filtration rate of 13 - 30 per/min. Excessive protein restriction has its adverse effect by causing malnutrition and

wasting, and hence RRT is advocated earlier in the progression of renal failure. The control of hyperlipidaemia should be advocated in all patients[53].

Regarding hypertension it is safe to say that the only intervention beneficial to patients with CRF is control of blood pressure, Two question arise –

a) the optimal level of blood pressure control, and

b) which anti-hypertensive drug should be used[54].

Most trials aim at a blood pressure of 120/75mm Hg with a mean of 92 in patients having more than 1gm per day proteinuria. Although not universally accepted there is evidence that angiotensin converting enzyme (ACE) inhibitors are useful. This has been proven in experimental animals. However, in diabetic and some non-diabetic nephropathies and anti-proteinuric effect can be achieved by non dihydropyridine, calcium antagonist such as dilthiazem and even blockers.

In patients with polycystic disease and in the elderly, ACE inhibitors may even accelerate the rate of decline in renal function and hence used cautiously. Patients genotype with ACE genotype 11 had a better response than with genotype DD. Hence a combined drug therapy may have to be advocated. What then may be the future?

The place of hormonal agents and autocoids together with the use of angiotensin receptor antagonists, endothelial reactive antagonists will have to be considered in the years to come.

Nephropathy has moved forward and research has become a necessity in tropical regions and should be done with all available resources.

Tropical renal failure into the next millenium and its relevance to internet needs mention[55]. Through internet there could be an exchange of ideas with developed countries and also the ability to co-ordinate research, with both developing countries of the tropics and the affluent countries. There is a necessity to emphasise the need of health programmes within a framework of the socio-economic factors in various countries and also influence current political ideaologies pertaining to renal medicine. The politicization of medicine further calls for constant dialogue and active participation in the health management programmes of government. Doctors should be made to pressurise and prevail upon policy makers into understanding the problems concerning renal failure in the tropics.

"Clinical research, whether it be the study of disease at the level of molecules and cells, or the maintenance of health in the community, will by the year 2000 enter the most rewarding era of its history" – David Wetherall, Professor of Medicine, Oxford.

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