Asia Pacific is a region of the world in or near the Western Pacific Ocean (Fig 1). It includes around 60% of the world’s population, which is growing,¹ and has the largest population density in the world. The social, cultural, economic, environmental, and religious diversity within this region is the highest in the world. Particularly striking is the disparity in economic development; only 7 countries (Japan, South Korea, Singapore, Taiwan, Brunei, Australia, and New Zealand) in Asia Pacific are classified as developed countries. The others are in various stages of development and are considered “emerging economies.” Most have agrarian economies, with a large number of people living in remote rural locations. Poorly managed economies, lack of skilled human resources and technology, weak infrastructure, and an inappropriate health policy framework obstruct improvements to health care delivery, as exemplified by failure to reach the health-related Millennium Development Goals.²

The exact number of patients with chronic kidney disease (CKD) in Asia Pacific is uncertain. In numeric terms, the region is home to the largest population of patients with untreated chronic kidney failure. The climatic, geographic, social, cultural, economic, and environmental diversity within this region is higher than in any other part of the world. Large parts of the region face a climate-related burden of infectious diseases. Infections contribute to the development and progression of CKD and complicate the course of patients with pre-existing CKD (especially those on dialysis therapy or who are immunosuppressed), increase the cost of CKD care, and contribute to mortality and morbidity. Kidney involvement is a feature of several infectious diseases prevalent in Asia Pacific. Examples include malaria, leptospirosis, scrub typhus, tuberculosis, hepatitis B and C virus, dengue hemorrhagic fever, and Hantaan virus infections. The contribution of infection-associated acute kidney injury to the overall burden of CKD has not been evaluated systematically. Research is needed to quantify the impact of infections on kidney health by undertaking prospective studies. Nephrologists need to work with infectious disease research groups and government infection surveillance and control programs. Am J Kidney Dis. 68(1):148-160. © 2016 by the National Kidney Foundation, Inc.

INDEX WORDS: Asia Pacific; chronic kidney disease (CKD); infections; infectious diseases; acute kidney injury (AKI); epidemiology; review.
infection associated with acute kidney injury (AKI) in Asia was \( \sim 52\% \). Importantly, 7% to 16% of patients went on to develop chronic kidney failure, and 11% to 19% were left with decreased kidney function despite being cured of the infection.8 Another recent study showed faster declines in glomerular filtration rates in patients who showed high titers of anti-leptospira antibodies, indicating past exposure to this organism.9

Asia Pacific also exhibits an enormous variation of climate and topography, from tropical to arctic and from the Himalayas to coral reefs. Most countries fall either completely or partially in the tropical zone. The tropical climate is characterized by high ambient temperatures and humidity and is conductive to growth of various life forms, making it a large reservoir for vectors responsible for disease transmission. Some of these climate-sensitive conditions include diarrheal diseases and vector-borne infections, major preventable causes of kidney diseases.10

The relationship with infection and chronic kidney disease (CKD) is bidirectional. Infections contribute to the development and progression of CKD but do not receive adequate recognition and complicate the course of patients with pre-existing CKD. They are more severe, detected late, and harder to manage; increase the cost of CKD care; and contribute to mortality and morbidity.11-13

We describe the burden of CKD in Asia Pacific with the possible links to infection and the impact of infections on patients with pre-existing CKD.

OVERVIEW OF CKD IN ASIA PACIFIC

Epidemiology

In Asia Pacific, the incidence and prevalence of chronic kidney failure and the resulting need for renal replacement therapies (RRTs) are increasing rapidly. Except for Japan, Taiwan, South Korea, Australia, and New Zealand, where RRT is widely available, access to this life-saving but expensive therapy is limited in other countries in the region. According to a recent report,14 of about 2.89 million people who needed RRT in Asia and Oceania in 2010, only 0.993 million received the therapy. This number is likely to grow in coming years, making it imperative to develop CKD detection and prevention programs.

The incidence and prevalence of earlier stages of CKD are uncertain, primarily because of the lack of large-scale epidemiologic studies. Published studies show figures ranging from 9% to 17%.15 The variations are explained by the different definitions of CKD. Studies that included hematuria (which might be a surrogate for infection-related proliferative glomerulonephritis [GN]) to define CKD generally show a higher CKD prevalence.16-18

Etiology

The etiologic spectrum of CKD is also not uniform in countries within the region. Despite the incessant increase in proportion of patients with CKD caused by diabetes, chronic GN and chronic interstitial nephritis remain the leading causes of CKD in several countries. Chronic GN remains dominant in China, Indonesia, and Malaysia,19-21 whereas a high frequency of chronic interstitial nephritis has been described from parts of South Asia.22-24 Infections play an important etiologic role in both these conditions. Some parts of the region report a high prevalence of CKD of unknown cause.22,24,25 The role of locally prevalent infections also
Several infectious diseases prevalent in Asia Pacific, such as malaria, leptospirosis, tuberculosis (TB), human immunodeficiency virus (HIV)/AIDS, dengue hemorrhagic fever, and Hantaan virus infections, affect the kidneys (Box 1). The primary presentation is in the form of AKI, either de novo or on the background of CKD. Of patients who recover from AKI, as many as 28% of those who had no existing CKD, infections often accelerate the rate of progression. In those with pre-existing CKD, infections often accelerate the rate of progression. Many of these patients have multiple comorbid conditions, making it difficult to dissect the role of kidney involvement on the overall outcome.

Kidney injury in infections prevalent in Asia Pacific may occur as a result of several mechanisms. These include direct invasion by the offending microorganism leading to cytopathic injury, as in pyogenic infections, TB, leptospirosis, and nematode infestations; through immune mechanisms involving microbial antigens that might lead to the generation of circulating or in situ immune complexes or cause perturbations in innate and cellular immunity, as in infection-related GN; and by systemic inflammatory response syndrome, hemodynamic disturbance, multiorgan failure, hemolysis, rhabdomyolysis, hepatorenal syndrome, and nephrotoxicity of antimicrobial therapy.

The following section describes specific infections that lead to kidney disease in Asia Pacific.

### INFECTION-RELATED CAUSES OF KIDNEY DISEASE IN ASIA PACIFIC

#### Viral Infections

**Hepatitis B Virus**

About 75% of the 350 million people affected with hepatitis B virus (HBV) worldwide are from Asia. The reported prevalence of kidney disease related to HBV infection closely aligns with the geographic distribution of HBV prevalence in the region, which ranges from 2.8% in South Korea to 20% in Taiwan and Vietnam. In a retrospective analysis of 11,618 kidney biopsies performed from 1987 to 2012 at a single center in Beijing, China, 3% were reported to have HBV-associated nephritis. Of the 3 primary forms of GN linked with HBV infection (membranous GN, membranoproliferative GN, and immunoglobulin A nephropathy), membranous GN is most commonly reported in Asian populations, particularly among children. In some areas, HBV-related disease accounts for up to 15% of all membranous nephropathy cases. By comparison, mesangial proliferative forms with IgA deposits appear to be more common in adults. An association of HBV infection has also been described with mixed cryoglobulinemia, polyarteritis nodosa, and focal segmental glomerulosclerosis. The introduction of nationwide HBV vaccination in China in 1992 led to significant decreases in childhood glomerulonephritis.

**Hepatitis C Virus**

Asia Pacific is home to 100 million of about 170 million individuals worldwide infected with hepatitis C virus (HCV). The majority are in the Western Pacific (62.2 million) and Southeast Asia (32.3 million). The prevalence of antibodies to HCV is estimated to range from 0.3% to 5.6% in New Zealand and Thailand, respectively. HCV hyperendemic parts of Japan, Vietnam, and Taiwan have prevalence rates of 12% to 58%. In contrast to HBV infection, HCV infection is marked by a silent onset and chronic course. The virus’ behavior and response to treatment vary according to its resistance.
genotype and host characteristics. Genotype 1, the most virulent form, is the most frequent form encountered in Australia and North Asia; genotype 6, in Southeast Asia; and the less virulent genotype 3, in India and Pakistan. There is a robust and probably causal association between chronic HCV infection and several chronic glomerular diseases. An autopsy study revealed glomerular lesions in 55% of HCV-infected individuals, including mesangial proliferative GN (17.6%), membranoproliferative GN (11.2%), and membranous nephropathy (2.7%). Recent population-based studies have shown a link between HCV infection and proteinuria. Some studies have reported a high prevalence of persistent proteinuria and hematuria.

**Hantavirus**

Infection with this zoonotic rodent-borne virus causes hemorrhagic fever with kidney and lung injury. Kidney disease is the dominant manifestation in Asia Pacific, presenting as AKI, proteinuria, and hematuria. RRT is needed in 30% to 40% of patients and is associated with high mortality. Large numbers of deaths have been reported from China and South Korea. Of those who recover from the acute phase, a significant proportion are left with residual decreased glomerular filtration rate and may develop hypertension.

**Bacterial Infections**

Bacterial infection continues to be a major health problem in many countries of Asia Pacific. Kidneys are particularly vulnerable to certain types of bacterial infections. In particular, there is the persisting high-frequency AKI in the setting of puerperal and postabortal sepsis secondary to poor obstetric care in the underdeveloped rural areas of Asia Pacific. In many hospitals, about one-third of all AKI cases are following obstetric complications. Of those who survive the infection, as many as 20% develop irreversible kidney failure due to acute renal cortical necrosis, and another one-third show incomplete renal recovery.

**Mycobacterial Infections**

TB and leprosy are the 2 common infections caused by mycobacteria. Both are endemic in South and Southeast Asia and may involve the kidneys.

**Tuberculosis**

TB is common in Southeast Asia, with an incidence of 211 per 100,000 population. Although the incidence is higher in Africa (281/100,000), Southeast Asia has the largest number of TB cases in the world (5.4 million in 2014). Involvement of the genitourinary tract is seen in 6% to 8% of all cases of TB, with males twice as likely as females to be affected. The infection reaches the kidneys through the bloodstream, but the involvement of the collecting system (urinary bladder and ureters) leads to obstructive nephropathy. When unrecognized, destructive caseous lesions involve the renal parenchyma, causing permanent loss manifesting as “putty kidney” (Fig 2). Renal TB can also present with progressive kidney injury due to granulomatous interstitial nephritis that may be difficult to distinguish from sarcoidosis. TB is the most common cause of AA (secondary) amyloidosis in the Indian subcontinent. Renal amyloid can develop several years after the diagnosis and treatment of TB. The diagnosis of TB is difficult due to unsatisfactory culture techniques and lack of the newer nucleic acid–based tests. Smear positivity in urine is unreliable for the diagnosis of genitourinary TB because the urinary tract can be colonized by environmental mycobacteria.
Leprosy

Despite a large reduction in prevalence, this disease remains endemic in several parts of South Asia and where cases with high bacillary load still occur. In a report of 122 cases from India, reduced creatinine clearance and proteinuria were common. Autopsy studies revealed a wide spectrum of renal lesions, including renal amyloidosis, GN, tubulointerstitial nephritis, and granulomatous disease (in decreasing order of frequency).

Protozoal Infections

Malaria

More than 2.2 billion people in Asia Pacific live in malaria endemic zones, representing about two-thirds of the world’s at-risk population. These include 6 of the top 10 countries worldwide with the largest at-risk populations: India, China, Indonesia, Bangladesh, Vietnam, and the Philippines. Of the 5 human malarial parasites—Plasmodium falciparum, Plasmodium vivax, Plasmodium knowlesi, Plasmodium malariae, and Plasmodium ovale—the first 3 are prevalent in the region and cause kidney disease.

Kidney involvement is mostly a feature of P falciparum infection. The usual presentation is with AKI. A small but significant proportion exhibit glomerular involvement, either acute nephritic syndrome or nephrotic syndrome. The prevalence of kidney involvement varies from <1% in uncomplicated infections to >50% in severe malaria. Blackwater fever, seen in the setting of glucose-6-phosphate dehydrogenase deficiency, is encountered among children infected with P falciparum malaria from Southeast Asia and parts of Northeastern India. Ingestion of quinine precipitates intravascular hemolysis, leading to AKI, which in turn substantially increases mortality risk. Provision of RRT to these patients presents a challenge in resource-constrained environments because modern methods such as continuous RRTs are often not available. In such situations peritoneal dialysis (PD) is often life-saving.

Previously considered benign, kidney involvement in P vivax infection is now being reported from South Asia, sometimes with severe and irreversible injury, especially in children. Kidney involvement in P knowlesi infection has been described from Thailand and Malaysia, where it has become the predominant cause of malarial kidney injury. This phenomenon likely represents a change in virulence characteristics of these 2 organisms and needs further studies.

The pathogenesis of kidney injury in malaria is multifactorial, with the main abnormality being hemodynamic alterations produced by unique properties of this parasite, which produces hemorrhagic changes leading to renal ischemia. Other factors include volume depletion, intravascular hemolysis, rhabdomyolysis, and altered levels of vasoactive cytokines. Histology usually shows acute tubular necrosis, with occasional pigment casts.

Leishmaniasis

This disease, also known as kala-azar, is mostly seen in rural areas of the Indian subcontinent. It is caused by Leishmania donovani, transmitted to humans by the bite of infected female sand flies. The organism predominantly involves the reticuloendothelial system, explaining the presentation with prolonged fever and hepatosplenomegaly. About 60% of patients exhibit proteinuria and urinary sediment abnormalities, implying the presence of proliferative GN, often associated with chronic tubulointerstitial damage. Antimonials used to treat the disease can worsen proteinuria and CKD.

Fungal Infections

Candida, Aspergillus, and Zygomyces species cause the main fungal infections that involve the kidney and urinary tract in Asia Pacific. The first 2 are usually ascending infections in patients on
long-term antibiotic therapy and with indwelling catheters, whereas the third is an angioinvasive infection that causes devastating kidney damage. Renal zygomycosis has been described mainly from India and presents as a febrile illness with invasion of renal vessels leading to tissue infarction.12,95,96 When bilateral (Fig 3), it causes irreversible kidney failure and carries high mortality despite antifungal therapy and tissue debridement.

Other Infections

**Lymphatic Filariasis**

Caused by *Culex* mosquitoes transmitting the nematodes *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori*, lymphatic filariasis is endemic to several countries in the region. India alone accounts for 40% of the global prevalence.97 Kidney involvement manifests as chyluria (passage of “milky” urine) and hematuria, which occur because of obstruction of the central lymphatic channels by filarial worms leading to dilatation and rupture of lacteals into the collecting system.98,99 Chylous urine tests positive for protein and may lead to a mistaken diagnosis of nephrotic syndrome.

A variety of glomerular lesions, independent of chyluria, has also been described in association with filariasis.100 A role for bacterial coinfection has been suggested. Once established, both chyluria and GN persist despite successful treatment of filariasis. Figure 4 shows a spectrum of renal abnormalities in filariasis.

**Scrub Typhus**

This has been identified by the World Health Organization (WHO) as a re-emerging disease in South Asia, Southeast Asia, and the Southwestern Pacific region. Scrub typhus is caused by the spirochete *Orientia tsutsugamushi*, which is transmitted by an infected trombiculid mite. Scrub typhus accounts for about 23% to 50% of all acute febrile episodes in endemic regions in Asia and has a case fatality rate of up to 50% if untreated.6,101 Kidney involvement is seen in ~80% of cases, with AKI in 53%.6,102 Because this complication has come to light only recently, the long-term kidney disease outcome in these patients is unknown.

**Leptospirosis**

Leptospirosis, the most common zoonosis worldwide, is prevalent in India, Southeast Asia, and Oceania.103,104 Caused by the spirochete *Leptospira interrogans*, the disease is transmitted when the organism present in animal urine comes in contact with abraded human skin or mucosal surfaces and gains entry to the circulation. Seroprevalence varies from 20% to 53% in endemic areas.105 Disease outbreaks are encountered during flooding in low-lying areas. Presentation as classic Weil disease is with an acute febrile illness with AKI, jaundice, myositis, and tissue hemorrhages.28 The spectrum of kidney injury includes mild proteinuria, urinary sediment abnormalities, tubular dysfunctions, and AKI primarily due to interstitial nephritis.67,106,107 A small proportion of survivors show persistent defects in tubular function and reduced glomerular filtration rates.108,109

**INFECTIONS IN PATIENTS WITH PRE-EXISTING CKD IN ASIA PACIFIC**

**Overview**

Infections remain common causes of morbidity, mortality, and hospitalization in patients with CKD, especially among those on dialysis therapy and after kidney transplantation. The pattern and outcome of infections are dependent on the local epidemiology and evolution of health care systems. Patients on hemodialysis (HD) therapy in resource-poor parts of the region with immature health care systems and lax regulatory standards are particularly vulnerable. Predisposing factors include late referral; reliance on central vein dialysis catheters, especially the uncuffed; frequent movement of patients between dialysis units; and poor adherence to infection control measures.12,110-113

**HBV and HCV Infections**

Despite increasing use of low-cost generic erythropoiesis-stimulating agents allowing a decrease in blood transfusion, infections with the 2 hepatitis viruses is a substantial problem in the dialysis population in many
countries of the region. Patients with CKD are often referred late and therefore are not immunized against HBV, putting them at risk for contracting the disease in HD units.\textsuperscript{114} Moreover, serologic assays rather than sensitive nucleic acid–based techniques including polymerase chain reaction are still used for screening. This leads to underdiagnosis of infection in the window period, increasing the risk for horizontal transmission.

In a recent study\textsuperscript{115} of dialysis registries of 10 countries in Asia Pacific that included 201,590 patients, the hepatitis B surface antigen positivity rate ranged between 1.3% and 14.6%, and HCV seroprevalence varied between 0.7% and 18.1%. A significant proportion of HCV RNA–positive patients were seronegative. HBV prevalence was similar between PD and HD populations in China, Hong Kong, Malaysia, and Thailand, but higher in PD patients in Japan and Taiwan and lower in PD patients in South Korea. For HCV, the prevalence was higher in HD than PD patients across the region (7.9% vs 3%). The seroconversion rate was greater in HD patients (0.1 vs 0.03 per 100 patient-years at risk).

In recent years, HCV infection has become a significant health threat in parts of Asia Pacific. A multicenter study from Vietnam of 8,654 patients found an HCV prevalence of 11% to 43%. Single-center studies from India have described prevalences of \textasciitilde 50%, leading to calls for isolation of HCV-infected HD patients to that practiced for those with HBV infection.\textsuperscript{116,117}

In addition to increasing the risk for chronic liver disease, the hepatotropic viruses predispose to hepatocellular carcinoma and death.\textsuperscript{118,119} HCV positivity has been shown to be a risk factor for premature death in the Japanese HD population, as well as those in Australia and New Zealand.\textsuperscript{118,120} The availability of effective antiviral agents for HBV and more recently HCV are expected to change the management and outcomes in these patients.

**Tuberculosis**

The incidence of TB in patients with CKD is 10 to 15 times higher than that in the general population,\textsuperscript{12,111} increasing to more than 50-fold among those on dialysis therapy and after kidney transplantation.\textsuperscript{121,122} About 7% to 10% of patients on maintenance dialysis therapy and 10% to 13% of transplant recipients develop overt TB. In some of the historic reports from the region, the overall mortality rate among organ transplant recipients with TB was 20% to 30%.\textsuperscript{121,122}

There are a number of issues of management of TB in the region. These include difficulties making a timely diagnosis of both active and occult TB, access to modern methods of detection and management of a potential transplant recipient with latent TB,\textsuperscript{123} minimizing the risk for donor-derived TB transmission to transplant tourists,\textsuperscript{124} dealing with the increasing prevalence of multidrug-resistant TB,\textsuperscript{125} and managing the interaction between anti-TB agents and post-transplantation immunosuppression. Mortality from TB can be almost eliminated by keeping a high index of suspicion, insisting on invasive investigations to establish the diagnosis, and instituting therapy promptly.\textsuperscript{126} Neither Mantoux testing nor the newer interferon \(\gamma\) release assays have been found useful for identifying latent TB before transplantation in endemic regions.\textsuperscript{127} New anti-TB drug regimens that exclude rifampicin have simplified the problem drug interactions altering the concentration of calcineurin inhibitors in transplant recipients.\textsuperscript{128}
Fungal Infections

In tropical countries, patients with CKD are at increased risk for fungal colonization because of the hot and humid climate, poor hygiene, and common use of broad-spectrum antibiotic therapy. A significant proportion develop clinical disease. The disease pattern, organ involvement, and presentation are influenced by stage of CKD, type of RRT (HD, PD, or kidney transplantation), and the local mycologic flora. The most common endemic mycoses in Oceania are histoplasmosis, penicilliosis, and sporotrichosis, whereas the dominant infections in tropical countries are caused by saprophytic and opportunistic fungi such as *Candida*, *Aspergillus*, and *Zygomycetes* species. There is a high (10%-14%) prevalence in PD patients of peritonitis caused by *Candida* species reported in India. Similarly, mucocutaneous fungal infections are frequent in kidney transplant recipients, seen in 60% to 72%. The organisms responsible include *tinea corporis*, *tinea cruris*, and *tinea versicolor* (55%-65%), followed by *Candida* (7%-9%) and *Cryptococcus* species (0%-1%). The incidence of tissue-invasive fungal infections among kidney transplant recipients is 4% to 7%. Overall, aspergillosis remains the most frequently reported invasive mold infection in patients with CKD and postransplantation patients within Asia Pacific. A high prevalence of zygomycosis has been reported from India. Delayed diagnosis because of the lack of specialized laboratories and failure to use invasive diagnostic tests increase the morbidity and mortality.

**CHALLENGES AND FUTURE DIRECTIONS**

Because of the link between diabetes, hypertension, and cardiovascular disease, CKD has been categorized under the broad heading of noncommunicable diseases. However, this paradigm might be inappropriate in large parts of the world, including Asia Pacific. We argue that the direct and indirect contribution of infection has a major impact on the onset and course of CKD in the region and deserves the attention of the research community and public health policymakers. The WHO has described several of the infections highlighted in this review as “neglected diseases,” meaning they receive less attention from the scientific community and pharmaceutical industry.

Infection control in large parts of Asia Pacific is limited by poverty, high population density, inadequate sanitary facilities, low uptake of vaccines, indiscriminate antimicrobial use leading to multidrug-resistant organisms, isolation from health care access, and periodic disasters and wars. In large parts of Asia Pacific with growing economies, land clearance and deforestation in the name of development have led to large-scale disruptions and loss of biodiversity, leading to the emergence of new strains of Hantaan viruses, dengue viruses, multidrug-resistant *Escherichia coli*, and artemisinin-resistant *Plasmodium* species, all of which have implications for kidney disease. Increased population mobility reduces the likelihood of geographic containment. Global warming and climate change are expected to have an adverse effect on the ecosystem, affecting the availability of clean air, potable water, sanitation facilities, sufficient food, and safe shelter. As a consequence, there has been a sharp increase in the number of outbreaks of infectious diseases in Asia Pacific (Fig 5).

The paucity of good-quality data limits accurate assessment of the impact of infections on CKD in the region. Most developing countries in the region do not have a systematic process for collecting data for patients with chronic kidney failure and earlier stages of CKD. Proper evaluation of the impact of kidney involvement on the infection cycle is needed. It is possible that early recognition and aggressive management of kidney complications might improve short- and long-term patient outcomes in patients with infections. This knowledge gap can only be bridged by prospective studies with particular attention to

**Figure 5.** Increase in total outbreaks and total number of infectious diseases causing outbreaks since 1950 in Asia Pacific countries. Reproduced from Morand et al. (Fig 5).
infections. Nephrologists need to establish linkages with infectious disease research groups and government infection surveillance and control programs. Infectious disease databases should collect data on the pattern and severity of kidney disease and its impact on short- and long-term outcomes, in particular the risk for CKD and its complications.

Strategies to combat infection in Asia Pacific need to take account of the local geography and climate. A cooperative approach between different countries of the region is also needed. For example, the failure of malaria eradication programs in India is explained in part by the reintroduction of the vector and organisms from neighboring countries, where similar eradication programs were not implemented simultaneously.¹⁴⁴

Lack of safe drinking water and adequate sanitation remain major threats to kidney health. The important contribution of repeated clinical or subclinical episodes of kidney injury related to recurrent diarrheal illnesses, especially in children and in agricultural workers who work all day in a hot and humid environment, has not been adequately studied. Lessons must be learned from the descriptions of Mesoamerican nephropathy from Central America,¹⁴⁵ where some local governments have provided shaded “rest areas” and instituted mandatory “water breaks” for these workers.¹⁴⁶ Inexpensive technology is needed for purifying water in rural areas to make it potable. Health education will help people change their drinking habits and will encourage hand washing and cleaning raw fruits and vegetables gathered from potentially contaminated fields. The solutions require changes in all aspects of health systems. Close collaboration is needed between physicians, public health professionals, policy makers, social activists, and the media. The successful eradication of smallpox from the globe and the near eradication of polio are encouraging examples that suggest that despite huge obstacles, these goals can be achieved.

ACKNOWLEDGEMENTS

Support: Dr Jha has grant support from the Department of Biotechnology, Government of India, and the Indian Council of Medical Research.

Financial Disclosure: Dr Jha has received research grants from Baxter International and GlaxoSmithKline. The other author declares that he has no relevant financial interests.

Peer Review: Evaluated by 2 external peer reviewers, the Feature Editor, and the Editor-in-Chief.

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