Community-Acquired Acute Kidney Injury in Asia

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Summary: Asia, the largest continent in the world, is heterogeneous in the ethnic, socioeconomic, and developmental status of its populations. A vast majority of it is poor with no adequate access to modern health care, making an accurate estimation of the nature and extent of acute kidney injury (AKI) difficult. Community-acquired AKI in otherwise healthy individuals is common, and the population developing AKI is younger compared with its counterparts in Europe or North America. The etiologic spectrum varies in different geographic regions of Asia depending on environmental, cultural, and socioeconomic factors. Some of the etiologic factors include AKI in relation to infectious diseases, intravascular hemolysis caused by glucose 6-phosphate dehydrogenase deficiency, poisonings caused by industrial chemicals or copper sulphate, animal venoms, natural medicines, heat stroke, and after complications of pregnancy. Preventive opportunities are missed because of failure to recognize the risk factors and early signs of AKI. Patients often present late for treatment, leading to multi-organ involvement and increased mortality. The exact etiologic diagnosis cannot be established in many instances because of a lack of appropriate laboratory support. Modern methods of renal replacement therapy are not universally available; and intermittent peritoneal dialysis is still widely practiced in many areas.

Keywords: *Acute kidney injury, Asia, acute renal failure, malaria, leptospirosis, snake bite*

Asia is the largest continent in the world, and home to more than half of the world population. It has countries such as China and India, with populations in excess of 1 billion each, and small countries such as Maldives and Bhutan with 0.3 and 0.6 million people, respectively. In contrast to the developed continents such as Europe and the Americas, Asia is extremely heterogeneous in terms of the ethnic composition and socioeconomic status of its populations. Some countries such as Japan, Korea, and Singapore have a high gross national income, are developed in terms of access to goods and services, and the population enjoys a high standard of living. In contrast, most other Asian countries have been grouped by the World Bank into a low-income group (per capita gross national income, ≤ US $905), and have limited access to many services including health care. A majority of the population is dependent on agriculture or manual labor for their income. The difference in living standards, prevalent cultural practices, and availability of health care determine the variations in disease patterns and management practices. The economic, human, and technical resources required for specialized treatment such as dialysis pose a major economic and political challenge. The public sector health care in these countries is organized in the shape of a pyramid, with primary health centers at the bottom, followed by intermediate-level hospitals, and referral hospitals at the top. Specialized care for kidney disease usually is available only at the major referral hospitals. There is a thriving private sector health care industry, but the treatment costs are quite high, and only the rich or those whose health care expenses are covered by their employers can afford treatment in these hospitals. Finally, indigenous health care delivery systems still are popular in rural Asia, and patients frequently

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are treated with herbs and potions. As described elsewhere in this issue, this often contributes to the burden of acute kidney injury (AKI) in the community.

Reliable statistics on the patterns and prevalence of AKI in Asia are not available, but AKI is the most common renal emergency encountered in Asian hospitals.[1-4] Comparative data suggest an increase in admissions as a result of AKI in Asian hospitals, possibly owing to increased awareness and referrals.[5-7] Community-acquired AKI in otherwise healthy individuals is far more common in the poorer countries of Asia, a characteristic they share with other countries of the world with underdeveloped economies.[5,8,9] About 0.1% to 0.25% of all admissions in Asian hospitals are for management of AKI.[4,10] In contrast, AKI is noted primarily in hospitalized patients with complex medical or surgical conditions in hospitals in the developed parts of the world.

Asian hospitals continue to be loaded with patients with AKI secondary to diarrheal diseases, septic abortions, and other infections and environmental conditions specific to the region. Malaria, diarrheal diseases, leptospirosis, intravascular hemolysis caused by glucose 6-phosphate dehydrogenase deficiency, snake bites, and insect stings together constitute the majority of AKI in India.[2,7] Also, patients in this region are younger compared with their counterparts in the West.[7] Lastly, the treatment facilities are grossly inadequate. Patients are referred late, only after renal failure becomes severe and complications set in. Often they require immediate dialysis, and have a high mortality rate. Intermittent peritoneal dialysis remains the mainstay of treatment in several areas[11-14]; hemodialysis facilities are limited to bigger cities. Modern methods of renal replacement therapy including hemofiltration are available in selected hospitals.[15] In a recent randomized trial between hemofiltration and peritoneal dialysis in Vietnam, the odds ratio for death was 5 in the group assigned to peritoneal dialysis. The cost of hemofiltration per survivor was less than half that of peritoneal dialysis, and the cost per life saved was less than one third.[16] AKI in patients with pre-existing chronic kidney disease constitutes an important entity. Indiscriminate nephrotoxic drug use and infections are important precipitating factors.[17] Most of the causes of AKI described elsewhere in the world are encountered in Asia as well, in intensive care units, and after sepsis or nephrotoxic drug use. Several causes, however, either are unique or are seen with increased frequency in Asia (Table 1). A few important ones are described later.

Table 1. Causes of AKI in Asia

Infections
Falciparum malaria
Leptospirosis
Hemorrhagic fever with renal syndrome
Dengue Fever
Zygomycosis
Infective diarrhea
Malioidosis
Typhoid
Scrub typhus
Chlamydia
Legionnaire's disease
Epidemic Rift Valley Fever
Plant toxins
Djenkol beans
Marking nut ingestion
Carp gallbladder or bile
Mushroom poisoning
Cleistanthus collinus poisoning
Triperygium wilfordii
Animal poisons
Snake bites
Wasp, hornet, and bee stings
Spider bite
Jellyfish sting
Scorpion sting
Chemical nephrotoxins
Copper sulphate
Ethylene glycol
Ethylene dibromide
Chromic acid
Intravascular hemolysis caused by glucose 6 phosphate dehydrogenase deficiency
Heat stroke
Natural disasters
Hemolytic uremic syndrome
Acute glomerulonephritis
Obstetric AKI

MALARIAL AKI

Introduction

Malaria, caused by the protozoan *Plasmodium* and transmitted by the Anopheles mosquito, has been described in ancient Chinese, Sumerian, Egyptian, and Indian Vedic and Brahmanic writings. The *Atharva Veda* specifically detailed the fact that fevers were particularly common after excessive rains or when there was a great deal of grass cover. Of the 4 plasmodium species, AKI is seen most frequently with *P falciparum*. This species predominates in warmer regions closer to the equator (parts of the Indian subcontinent, Myanmar, Sri Lanka, Malaysia, Indonesia, and Thailand) and causes intense year-round transmission. In addition to being a burden to the native communities, malaria is a danger to nonimmune travelers to endemic areas. The overall prevalence of AKI is less than 1%, but may increase to 60% in severe infections.[18] The incidence among those living in endemic areas is 2% to 5%, but 25% to 30% of nonimmune visitors get renal failure.

Clinical Features

Malaria is a common cause of fever. The classic paroxysms with spiking fever and rigors are rare. Other symptoms include malaise, myalgia, headache, and chills, and the disease can be confused for a viral illness. Nausea, vomiting, and hypotension are common in nonimmune individuals. Severe infection may involve several vital organs including the central nervous system, manifesting with deep coma and seizures, noncardiogenic pulmonary edema, shock, and disseminated intravascular coagulation. AKI usually is seen by the end of the first week and is nonoliguric in 50% to 75% of cases.[19,20] In more than 75%, AKI is associated with cholestatic jaundice. It usually is hypercatabolic, with a rapid increase in creatinine values.[21] Other manifestations include nonnephrotic proteinuria, microscopic hematuria, hemoglobinuria, and dyselectrolytemia. The clinical picture may resemble other tropical infections including leptospirosis, scrub typhus, and Hantavirus infection. Diagnosis can be established by the demonstration of asexual forms of the parasite in peripheral blood smears stained with Giemsa stain. Staining with the fluorescent dye acridine orange allows a more rapid diagnosis. Recently, simple but specific antibody-based card tests that detect *P falciparum*–specific histidine-rich protein 2 or lactate dehydrogenase antigens in finger-prick blood samples have been introduced. They allow differentiation of falciparum from nonfalciparum malarias, but can remain positive for several weeks after acute infection. A scoring system based on the number of organ systems involved has been suggested for judging the severity and predicting outcomes in falciparum malaria.[22]

Histology

Acute tubular necrosis is the most common histologic lesion. Pigment casts may be seen in tubular lumina in patients with intravascular hemolysis. Varying degrees of interstitial edema and mononuclear cell infiltrate are common accompaniments.[19]

Pathogenesis

Disease severity is linked with the intensity of infection. Prommano et al[23] found a higher parasite load in the liver of patients with AKI. The most important pathogenetic factor in the genesis of malarial AKI is the hemodynamic changes caused by altered erythrocyte rheology. The infected cell becomes more spheric and less deformable as a result of formation of membrane protuberances or knobs on the cell surface. These knobs extrude a strain-specific adhesive-variant protein of high molecular weight that mediates attachment to receptors on venular and capillary endothelium, causing a phenomenon called *cytoadherence*. The major adhesive protein family is called *plasmodium falciparum erythrocyte membrane protein*. These cell-surface receptors for these knobs include CR-1, glycosaminoglycans, intercellular adhesion molecule-1, chondroitin sulfate B, CD36, PECAM-1/CD31, thrombomodulin, E- and P-selectins, and vascular cell adhesion molecule-1. Some of these are expressed constitutively, whereas others are induced by inflammatory mediators released in severe disease. Infected erythrocytes also adhere to uninfected red cells, platelets, monocytes, and lymphocytes. These aggregated and sequestered red cells interfere with micro-

circulatory flow. This phenomenon is unique to *P falciparum* and has not been observed with other species.

The parasite also induces the expression of several novel antigens on the surface of host cells by exposing the cryptic erythrocyte antigen and inserting antigens of parasite origin. These lead to activation of both Th1 and Th2 arms of the immune response and release of several cytokines that further potentiate the inflammatory response. *P falciparum* also activates the alternate complement pathway and intrinsic coagulation cascade.[24] Similar to sepsis syndrome, there is generalized vasodilatation and altered renal blood flow.[24,25] Rhabdomyolysis also has been described.[26]

Jaundice increases the incidence and severity of AKI in malaria.[27] An interesting observation is the relative resistance to renal injury in those with pre-existing helminthic infections. In one study, the adjusted odds ratio of development of AKI was 0.16; the investigators postulated that the protection was the result of reduced parasite sequestration and obstructive jaundice.[27]

Management

Mortality from malarial AKI varies between 10% and 40%.[19] Severe falciparum malaria requires intensive nursing care and careful multidisciplinary care. Formation of special teams has decreased the mortality rate by two-thirds in some countries.[28] Prompt assessment of volume status, blood glucose level, and acid-base status are essential. All patients with severe *P falciparum* infection should be presumed to have chloroquine-resistant infection. The cinchona alkaloids (quinine or quinidine) are the mainstay of treatment because of their activity against chloroquine-resistant strains. Quinine often causes hyperinsulinemia and hypoglycemia and many centers recommend administration of a continuous infusion of 5% to 10% dextrose to all patients.

Compounds derived from artemisinin (isolated from the Chinese herb *Artemisia annua*) such as artesunate, artemether, and arteether are particularly valuable in areas with quinine resistance and in patients with recurrent quinine-induced hypoglycemia. All patients should receive gametocidal therapy (tetracycline or pyrimethamine/sulfadoxine). Mefloquine, halofantrine, atovaquone, artemisinin, and fansidar derivatives are possible alternatives for resistant falciparum malaria.

Patients with evidence of hemolysis should receive adequate hydration and parenteral sodium bicarbonate to alkalinize the urine (pH $>$ 7.0). Earlier studies found dopamine and frusemide to be beneficial in maintaining the renal blood flow and urine volume in patients with serum creatinine levels of less than 5 mg/dL. Renal failure usually is hypercatabolic, and frequent dialysis may be needed.[29] Hyperkalemia should be watched for and adequately treated. The peritoneal microcirculation is impaired as a result f clogging with infected erythrocytes and vasoconstriction, reducing the efficacy of peritoneal dialysis. However, in practice, peritoneal dialysis is simple to perform and more easily available than hemodialysis. Continuous peritoneal dialysis has been shown to lower the blood urea and serum creatinine concentrations. In a recent comparative trial in Vietnam between state-of-the-art continuous venovenous hemofiltration and suboptimal peritoneal dialysis using a rigid catheter and an open drainage system, the former was associated with quicker resolution of acidosis and azotemia, and reduced risk of death and subsequent dialysis.[7]

LEPTOSPIRAL AKI

Leptospirosis, the most widespread zoonosis in the world, is prevalent in parts of India, Indonesia, Cambodia, Thailand, Vietnam, and the Philippines.[30,31] The animal hosts include rats, mice, gerbils, hedgehogs, foxes, dogs, cattle, sheep, pigs, and rabbits. Even asymptomatic animals carry a high number of organisms ($>10^{10}$/g) in their kidneys, and shed leptospira in urine for years. Human infection occurs incidentally either by direct contact with the urine or tissue of an infected animal or indirectly through contaminated water, soil, or vegetation. The usual portals of entry are abraded skin and exposed mucosae. Leptospirosis is an occupational hazard in coal miners; sewage, abattoir, and farm workers; and in the aquaculture industry.

The genus *Leptospira* contains only one species, *L interrogans*, subdivided into 2 complexes:

the pathogenic *L interrogans* strains, and *L biflexa*, containing the saprophytic strains. Disease occurs throughout the year, with an increase in the incidence during or soon after the rainy season, especially after floods. Adult men are affected most frequently.

Clinical Features

The manifestation varies from subclinical infection and self-limited anicteric febrile illness to severe and potentially fatal disease.[30,31] Symptoms appear 1 to 2 weeks after exposure and typically are biphasic in character. The initial (leptospiremic) phase is characterized by high fever with chills, headache, and severe muscle aches and tenderness. Renal failure develops in the second (immune) phase, when patients also have progressive jaundice, epistaxis, hemoptysis, gastrointestinal bleeding, hemorrhagic pneumonia, and bleeding into the adrenal glands.

AKI occurs in 20% to 85% of cases[32-36]; the combination of renal failure and cholestatic jaundice constitutes *Weil's syndrome*. In about half the cases, renal failure is associated with polyuria and hypokalemia along with increased fractional excretion of potassium. Khositseth et al[37] showed renal magnesium and phosphate wasting in patients with leptospiral AKI and recommended frequent measurement of magnesium and phosphate levels in both serum and urine. Renal failure is mild and nonoliguric in anicteric patients.[38] Hypotension is noted in more than 60%[39] and often is unresponsive to volume expansion and inotropic support. These patients are more likely to have pulmonary complications.[38] Hemorrhagic manifestations include epistaxis, hemoptysis, gastrointestinal bleeding, hemorrhagic pneumonitis, and bleeding into the adrenal glands.

Diagnosis is based on either culture or serology.[40] Organisms can be isolated on blood culture during the first phase and later from urine. Growth takes up to 4 weeks in Fletcher's or Stuart's semisolid media. The macroscopic agglutination test or the slide test can be used as a screening test, but is not specific. The benchmark is the microscopic agglutination test, but this is complex and requires maintenance of live Leptospira cultures. An IgM-specific dot enzyme-linked immunosorbent assay has been found to be specific in diagnosing leptospirosis in endemic areas. Urinalysis during the leptospiremic phase reveals mild proteinuria and hyaline and granular casts.

Histology

The kidneys typically are swollen[30,31] and may be bile stained. The main light microscopic lesions are interstitial edema and infiltration with mononuclear cells and eosinophils.[41] Mild and transient mesangial proliferative glomerulonephritis with C3 and IgM deposition may be observed.[42]

Pathogenesis

Renal involvement results from direct invasion of the renal tissue by the organism, leading to liberation of enzymes, metabolites, and endotoxins, and complement activation.[43] Ultrastructural studies after inoculation of *L pomoma* into mice showed the organism penetrating the glomerular capillary lumen at day 2, in the interstitium at days 4 to 8, eliciting edema and infiltration into the proximal tubular cells by day 10, and into the lumen by day 14.[31] Several leptospiral outer-membrane proteins have been localized to proximal tubules and interstitium of infected animals. Renal damage probably results from the liberation of bacterial enzymes, metabolites, and endotoxins, and complement-induced renal injury.[43] The addition of leptospira endotoxin to human macrophages induces tumor necrosis factor-α. The glycoprotein component of endotoxin could inhibit the renal Na-K adenosine phosphatase, which in turn affects the apical Na-K-Cl cotransporter, leading to potassium wasting. An up-regulation of nuclear factor-κB binding to DNA was noted on addition of outer-membrane extracts from pathogenic serovars to cultured medullary thick ascending limb cells. This was accompanied by an increase in the message for inducible nitric oxide synthase, monocyte chemoattractant protein-1, and tumor necrosis factor-α. Alterations in intravascular volume, hemoglobinuria, and myoglobinuria also contribute.[38,44] The tubules develop insensitivity to the action of antidiuretic hormone (ADH).

Management

Leptospirosis is a self-limiting disease and patients with mild cases recover spontaneously. The emphasis is on symptomatic measures, together with correction of hypotension and fluid and electrolyte imbalance. Crystalline penicillin or doxycycline shorten the duration of fever and hospital stay and may hasten amelioration of leptospiruria. Patients with renal failure need close monitoring and dialysis when necessary. A combination of dopamine and furosemide was useful in producing early diuresis and faster renal function recovery in patients with a serum creatinine level of 2.4 to 5.4 mg/dL.[45] Continuous venovenous hemofiltration, plasmapheresis, and exchange transfusions are beneficial in decreasing blood levels of cytokines and mediators.[39,46] Peritoneal dialysis still is used in some areas.[47] Renal failure was an important cause of death in the predialysis era, but death usually now is secondary to internal hemorrhage or myocarditis. Poor prognostic indices include increasing age, jaundice, pulmonary complications, hyperbilirubinemia, diarrhea, hyperkalemia, pulmonary rales, or hypotension on admission.[48,49] Survivors may show residual tubular dysfunction, such as a defect in the concentrating ability.

ZYGOMYCOSIS

Zygomycosis is a rare opportunistic infection caused by fungi of the order *Mucorales* and genera *Rhizopus*, *Absidia*, and *Rhizomucor*. Organ involvement occurs through vascular invasion, leading to thrombosis of large and small arteries, and infarction and necrosis of the affected organ. The major presentations include rhinocerebral, pulmonary, gastrointestinal, and disseminated forms. Renal involvement usually is occult and detected at autopsy. A form of primary renal mucormycosis involving major renal vessels has been described primarily from India.[50,51] Bilateral involvement leads to oliguric AKI. The condition usually develops in otherwise immunocompetent individuals; presentation is with fever, lumbar pain, pyuria, and oliguria. Ultrasound and computed tomography (CT) scan reveal enlarged kidneys with perirenal collection and/or intrarenal abscesses.[50,51] The diagnosis can be confirmed by demonstration of hyphae in the material obtained by aspiration or percutaneous biopsy. The only definitive treatment is extensive debridement of affected tissue, which may include bilateral nephrectomy, and systemic antifungal therapy with amphotericin B. Bilateral renal mucormycosis carries an extremely poor prognosis.[50,51] The exact pathogenesis of this condition is unclear.

HEMORRHAGIC FEVER WITH RENAL SYNDROME

Hantaan virus was the first recognized etiologic agent of hemorrhagic fever with renal syndrome (HFRS),[52] and other agents such as Puumala virus, Dobrava virus, and Seoul virus were discovered later. Approximately 150,000 HFRS cases are estimated to occur annually worldwide, most in Asia. The disease is characterized by high fever, headache, abdominal and back pain, bleeding tendency, and renal failure, and produces typical febrile, hypotensive, oliguric, diuretic, and convalescent phases.

Renal failure is nonoliguric in about 60% of cases. Oliguric patients require more dialysis and have a higher mortality rate. High leukocyte count, thrombocytopenia, aspartate aminotransferase level, and microscopic hematuria are predictive markers for the subsequent development of oliguric AKI in HFRS.[53] Intravenous ribavirin is effective in reducing the incidence of renal failure and mortality if started within 4 days of the onset of symptoms.[54]

MELIOIDOSIS

Melioidosis encompasses a broad spectrum of disease processes caused by *Pseudomonas* pseudomallei and is encountered in Vietnam, Thailand, and Malaysia. AKI has been described in about 60% of patients with acute septicemic melioidosis in Thailand.[55]

The presentation is with fever, productive cough, and marked tachypnea. Renal failure generally is oliguric and hypercatabolic. Pre-existing diabetes or alcoholic liver diseases are noted in more than 50% of patients with renal failure.[55] Characteristic features are a high blood urea nitrogen/creatinine ratio, hyperbilirubinemia,

hyponatremia, and hypoalbuminemia. Multiorgan dysfunction is common and the mortality rate approaches 90%. Diagnosis is established by demonstration of the organism in exudate material with methylene blue or Gram stain. Treatment is with ceftazidime at a dose of 120 mg/kg/d for about 1 month. Renal histology shows acute tubular necrosis, interstitial nephritis, and microabscesses.[55]

OTHER INFECTIONS

AKI also has been described sporadically with dengue fever,[56,57] scrub typhus,[58] *Chlamydia*,[59] legionnaire's disease,[60] and epidemic rift valley fever.[61] The number of cases is too few to draw any meaningful conclusion about their natural history or pathogenesis.

AKI CAUSED BY ANIMAL, PLANT, AND CHEMICAL TOXINS

Natural medicines form a special class of nephrotoxins encountered in traditional societies. In many tribal populations, these agents are prescribed by practitioners of traditional systems of medicine. The popularity of these healers is directly related to a combination of ignorance, poverty, lack of medical facilities in rural areas of the tropics, and widespread belief in indigenous systems of medicine.[62]

SNAKE BITE

Snake bite is an occupational hazard in the rural parts of Asia. AKI develops after bites by snakes of the viper family such as Russell's viper, saw-scaled viper, puff adder, rattlesnake, tiger snake, green pit viper, *Bothrops jararaca*, boomslang, gwardar, dugite, *Hypnale hypnale*, and *Cryptophis nigrescens*.[63-65] The incidence of AKI after Russell's viper or *E carinatus* bites varies from 13% to 32% in India,[66] and from 1% to 27% elsewhere.[67,68]

Clinical Features

Manifestations depend on the dose of venom injected; and vary from mild local symptoms to extensive systemic envenomation. Pain and swelling of the bitten part appear within minutes and may be followed by blister formation and ecchymosis. Bleeding from various sites is seen in 65% of cases and may be severe enough to produce shock. The blood is incoagulable in patients with severe systemic envenomation. Renal failure is heralded by oliguria or anuria, developing within a few hours to as late as 96 hours after the bite.[66,69,70] About half the patients give a history of passage of cola-colored urine. Nonoliguric renal failure is seen in less than 10% of cases. Oliguria usually lasts for 4 to 15 days, and its persistence indicates acute cortical necrosis.[65]

Investigations show coagulopathy, with hypofibrinogenemia; reduction of factors V, X, and XIIIA, protein C, and antithrombin C; and increased fibrin degradation products. Other findings include leukocytosis and increased hematocrit caused by hemoconcentration.

Histology

On gross examination, the kidneys are normal or slightly enlarged, and the surface may show petechial hemorrhages. Light microscopy shows acute tubular necrosis with hyaline or pigment casts in 80% of cases.[65] Varying degrees of interstitial edema, infiltration with eosinophils, mast cells and hyperplastic fibroblasts, and scattered areas of hemorrhage may be seen.[71] Electron microscopy reveals dense intracytoplasmic bodies representing degenerated organelles in the proximal tubules. Sitprija and Boonpucknavig[72] showed electron-dense mesangial deposits in patients bitten by cobras and green pit vipers. Acute interstitial nephritis, necrotizing vasculitis involving interlobular arteries, and crescentic glomerulonephritis may be seen occasionally.[73,74] Acute cortical necrosis carries the worst prognosis and is seen in about 20% to 25% of cases after Russell's viper and *E carinatus* bites.[66]

Pathogenesis

Pathogenic mechanisms include direct nephrotoxicity, hypovolemia, hemolysis, myoglobinuria, and disseminated intravascular coagulation. Injection of venoms of *B jararaca*, *Agkistrodon piscivorus*, and rattlesnake induces increased excretion of tubular enzymes and acute tubular necrosis in rats.[75] Russell's viper venom causes destruction of the glomerular filter, lysis of ves-

sel wall, and tubular injury in experimental animals. Vasculotoxic factors have been isolated from the venoms of several snakes, including *E carinatus*, *Vipera palastinae*, *A halys*, *B jararaca*, and Habu snake. Hypotension and circulatory collapse secondary to bleeding and release of kinins and depression of the medullary vasomotor center or the myocardium play a significant pathogenetic role.

Severe hemolysis has been observed after bites by Russell's viper and *E carinatus* bites in human beings and experimental animals.[76] The hemolysis results from the action of phospholipase A_2, and a basic protein called *direct lytic factor*. Microangiopathic hemolytic anemia has been recorded after *A rhodostoma*, Russell's viper, puff adder, and gwardar bites. Disseminated intravascular coagulation has been observed in experimental animals as well as in patients bitten by viper snakes. Infusion of Russell's viper or *E carinatus* venom into rhesus monkeys leads to disseminated intravascular coagulation.[65] The procoagulant factors in the venom activate factors V and X, and the subsequent activation of the coagulation cascade leads to rapid thrombin formation.[77] The fibrinolytic activity is caused by either direct action of the venom or a physiologic response to fibrin deposition. Phospholipase A_2 also leads to platelet aggregation. The demonstration of fibrin thrombi in the renal microvasculature, both in clinical and experimental studies, confirms the role of disseminated intravascular coagulation in the genesis of renal lesions.[66,69]

Management

The basic therapeutic approach to renal failure after snake bite is the same as that for AKI owing to any other cause. Early administration of antivenom is vital; delay results in a steep increase in the antivenin dose requirements. Indications include incoagulable blood, spontaneous systemic bleeding, intravascular hemolysis, local swelling involving more than 2 segments of the bitten limb, and a serum fibrin degradation products (FDP) concentration greater than 80 μg/mL. Knowledge of the offending snake species allows administration of monovalent antivenom wherever this is available. Immunodiagnostic techniques are helpful in identification of the venom antigen. Enzyme-linked immunosorbent assay has been used extensively in rural Thailand for this purpose.[78] The currently available test, however, is not quick enough for clinicians. Because only polyvalent antivenom is available in most parts of Asia, precise identification of the snake is not essential for management. Indian studies recommend initial administration of 20 to 100 mL of antivenom, followed by a repeat dosage of 25 to 50 mL every 4 to 6 hours until the effects of systemic envenoming disappear.[79,80] A simple way to monitor the efficacy is by monitoring whole blood clotting time 3 to 4 times every day. Coagulability generally is restored within 6 hours of an adequate dose. The test must be monitored for at least 3 more days because delayed absorption of the venom could lead to recurrence of the coagulopathy. Immunoassays permit serial estimation of venom levels, and are useful in guiding antivenom therapy. Other therapeutic measures include replacement of blood loss with fresh blood or plasma, maintenance of electrolyte balance, administration of tetanus immunoglobulin, and treatment of pyogenic infection with antibiotics. The prognosis is good in patients who receive adequate doses of antivenom. A recent study showed the outcome to be better after hemodialysis than peritoneal dialysis.[81] The overall mortality rate is about 30%.[66]

BEE, WASP, AND HORNET STINGS

Honey bees, yellow jackets, hornets, and paper wasps are stinging insects belonging to the order *Hymenoptera*. An isolated sting causes just a local allergic reaction, but occasional attack by a swarm of insects introduces a large dose of the venom sufficient to cause systemic symptoms.[82-84] These include vomiting, diarrhea, hypotension, loss of consciousness, and AKI. Patients with renal failure have been reported to have received from 22 to more than 1,000 stings. AKI develops primarily secondary to hemolysis and/or rhabdomyolysis. Hemolysis results from the action of a basic protein fraction and melittin and phospholipase A present in the venom. Rhabdomyolysis has been attributed to polypeptides, histamine, serotonin, and acetylcholine. A direct nephrotoxic role of these ven-

oms also has been suggested. Renal biopsy reveals acute tubular necrosis.[7]

OTHER ANIMALS

Isolated instances of AKI have been reported after spider bites, and stings by the scorpion, jellyfish, and the giant centipede.[85] Although the latter two give rise to intravascular hemolysis, renal failure after scorpion bite may result from disseminated intravascular coagulation and massive bleeding into various organs. Even a single spider bite may introduce enough venom to produce renal failure, especially in children. Venom of the spider *Sicarius* also causes disseminated intravascular coagulation.

DIARRHEAL DISEASES

AKI secondary to diarrhea is encountered mainly among children, although adult cases also are seen, especially when the initial rehydration is suboptimal.[12] It is prevalent in rural areas and urban slums inhabited by poverty-stricken individuals where sanitation is poor and often potable water is not available. Diarrheal AKI constitutes 35% to 50% of all children dialyzed for AKI.[86-88] The incidence increases during summer and rainy (monsoon) seasons. The most striking feature is dehydration. Small children present with lethargy, depression of the fontanelle, sunken eyeballs, altered sensorium, and oliguria. Urine output improves after fluid replacement in 20% to 25% of cases. Loss of bicarbonate and potassium leads to metabolic acidosis and hypokalemia. The clinical picture often provides a clue to the nature of the causative organism. Vomiting is an early feature of rotavirus diarrhea. Loose watery stools indicate infection with enterotoxigenic *Escherichia coli* or *Vibrio cholerae*. Fever, cramps, tenesmus, and blood and mucus in stools suggest *Shigella, Salmonella*, or enteroinvasive *E coli* infection. The diagnosis of cholera can be confirmed by microscopic demonstration of the highly motile vibrios in a hanging drop preparation; culture is necessary for confirmation of other organisms.

Early and adequate fluid replacement is the cornerstone of therapy. Widespread use of the oral rehydration solution recommended by the World Health Organization (20 g glucose, 3.5 g sodium chloride, 2.5 g sodium bicarbonate, and 1.5 g of potassium chloride dissolved in 1 L of clean preboiled and cooled water) has led to a significant decline in the mortality rate from this condition. Intravenous rehydration with Ringer's lactate may be required in patients with severe dehydration, persistent vomiting, or paralytic ileus. Established AKI usually is treated by peritoneal dialysis[89] where pediatric hemodialysis facilities are not available. Hypokalemia may worsen as the metabolic acidosis is corrected, and large amounts of potassium may be required to prevent life-threatening cardiac arrhythmias. Because the commercial peritoneal dialysis fluid is potassium-free, potassium should be replaced through an intravenous or intraperitoneal route. Mortality is higher in females, infants, and those with dyselectrolytemia and severe dehydration at admission.[90] Acute tubular necrosis is the most common histologic lesion, but acute renal cortical necrosis is encountered occasionally.

HEMOLYTIC-UREMIC SYNDROME

Hemolytic-uremic syndrome is currently the most common cause of pediatric AKI in many areas, and is responsible for 25% to 55% of all cases in Asian countries.[91-94] This condition is seen mainly in pre-school–age children, and is less common in adults. The main feature is oliguric renal failure, preceded by a diarrheal prodrome in about 70%. Neurologic involvement is seen in 30% to 50% of cases. Examination reveals pallor and mild icterus. Renal failure is severe and requires a prolonged period of dialysis. Diagnosis is clinched by demonstration of fragmented erythrocytes on the blood smear and thrombocytopenia. Supportive evidence includes unconjugated hyperbilirubinemia, increased plasma lactate dehydrogenase levels, and increased fibrin degradation products. *E coli* O157:H7 outbreaks causing hemolytic uremic syndrome (HUS) have been described from China,[95,96] but the primary etiologic organism in the Indian subcontinent is *Shigella*.[97,98] The histologic hallmark of this condition is thrombotic microangiopathy in the renal vasculature. Histology shows disproportionately high involvement of arterioles and small arteries with severe inti-

mal proliferation and luminal stenosis from Asian reports.[91,99] Up to 40% develop patchy or diffuse renal cortical necrosis.[91]

The treatment mainly is supportive. Plasma infusions or exchange are used infrequently; the outcome is poor, with a mortality rate of 60%.[100] Of those who show recovery, a significant proportion is left with residual renal dysfunction and eventually progress to end-stage renal disease.

INTRAVASCULAR HEMOLYSIS AND GLUCOSE 6-PHOSPHATE DEHYDROGENASE DEFICIENCY

Glucose 6-phosphate dehydrogenase (G6PD) is a key enzyme that protects erythrocytes from oxidant stresses. Deficiency caused by mutations in the *G6PD* gene causes intravascular hemolysis. AKI is seen in 5% to 10% of cases.[3,101-103] The gene is located on the X chromosome, and hence males carrying the affected gene develop more severe hemolysis. The severity also depends on the nature of the genetic defect. The G6PD variant (Mediterranean) in parts of India and Pakistan leads to hemolysis only in response to oxidative stress.[104] Individuals deficient in the enzyme cannot maintain an adequate level of reduced glutathione, leading to precipitation of oxidized hemoglobin in red blood cells, which then are sequestered and lysed. Hemolytic crisis develops within hours of exposure to the stress, most commonly by drugs, toxins or infections. Incriminated are pharmacologic agents such as primaquine, sulfonamides, acetylsalicylic acid, nitrofurantoin, nalidixic acid, furazolidone, niridazole, doxorubicin, and phenazopyridine; toxic compounds such as naphthalene balls; infections such as viral hepatitis, rickettsia, typhoid, and urinary tract infections; and severe metabolic acidosis of any cause. Additional risk factors such as dehydration and other nephrotoxic agents increase the likelihood of AKI. Passage of dark (cola)-colored urine followed by oliguria are the most common symptoms.[102] Oliguria lasts for about a week, after which the patient may enter a diuretic phase. The diagnosis should be considered in any individual who develops renal failure after an acute hemolytic episode, and the patient should be questioned thoroughly about any possible exposure to oxidant agents. Hemolysis is evidenced by a decrease in the hematocrit level, along with an increase in plasma-free hemoglobin level, unconjugated hyperbilirubinemia level, and a decline in the haptoglobin level. Estimation of the G6PD level in the erythrocytes by the fluorescent spot test confirms the deficiency. Normally the enzyme activity decreases as the cells age, and older cells with the lowest enzyme activity are destroyed first in a crisis. This can give false-negative test during a hemolytic episode when the surviving red cell population consists of younger erythrocytes, especially in those with mild deficiency. The test should be repeated after the patient has recovered from the acute episode to enable the correct diagnosis.

Renal histology shows acute tubular necrosis. The tubules may contain pigmented hemoglobin casts.

COPPER SULPHATE POISONING

Renal failure after the ingestion of copper sulphate with suicidal or accidental intent has been reported from Indian subcontinent.[105,106] Its distinctive blue color and strong metallic taste preclude its use for homicidal purposes. The incidence has shown a significant decline after 1980.[2]

Copper sulphate is a strong corrosive, and produces symptoms within minutes of ingestion. Metallic taste, excessive salivation, burning retrosternal and epigastric pain, nausea, and repeated vomiting are the initial features. The vomitus is blue–green and turns deep blue on addition of ammonium hydroxide, allowing it to be differentiated from bile. Diarrhea, hematemesis, and melena follow. Jaundice, hypotension, convulsions, and coma may develop in severe cases. Acute pancreatitis, myoglobinuria, and methemoglobinemia also have been reported.[106,107] Renal failure is seen in 20% to 25% of cases and is invariably oliguric. Hemoglobinuria may be seen in about 40% of cases. Diuresis ensues after 7 to 10 days and is followed by complete renal recovery.

Histology usually shows acute tubular necrosis, with predominant involvement of proximal tubules. Hemoglobin casts may be noted in pa-

tients with intravascular hemolysis. Acute cortical necrosis has been seen rarely.

Copper can produce considerable oxidant stress and interferes with the activity of several key enzymes such as Na-K adenosine triphosphatase, G6PD, glutathione reductase, and catalase. Direct nephrotoxicity, severe hemolysis caused by copper, and hypovolemia secondary to fluid loss are the main factors for kidney injury. In experimental animals, copper sulphate produces toxic damage to the proximal tubules.

Management entails gastric lavage using 1% potassium ferrocyanide, which leads to the formation of insoluble cupric ferrocyanide. Egg whites or milk can be administered as an antidote. Emesis should not be tried. Any volume deficit should be corrected quickly. Hyperkalemia may be severe and sustained because of the ongoing hemolysis and requires early and frequent dialysis.

ETHYLENE GLYCOL POISONING

Diethylene and polyethylene glycols have been used as cheap substitutes of propylene glycol as vehicle in pediatric syrup preparations. Epidemics of diethylene glycol–induced AKI have been reported from India and Bangladesh.[108-110] In one large study, 236 deaths were recorded among 339 children with unexplained AKI in a children's hospital in Dhaka (Bangladesh). A total of 51 children had ingested a brand of paracetamol known to contain diethylene glycol, whereas 85% of the remaining patients had ingested an unknown elixir for fever.[108] In another report,[109] 14 patients died of AKI after administration of a glycerol to decrease intracranial or intraocular pressures. Analysis of this preparation showed it to be 70% ethylene glycol. Autopsy revealed acute cortical necrosis as the most frequent lesion.

ETHYLENE DIBROMIDE POISONING

Ethylene dibromide (EDB) is a pesticide fumigant and is absorbed from skin, gastrointestinal tract, and intestinal mucosa. Accidental poisoning has been reported in those exposed to large quantities of EDB. In one instance, EDB was mistaken for ethylene bromide and administered as an anesthetic. Suicidal poisoning also has been reported. AKI and hepatitis are the chief manifestations.[111,112] The mortality remains very high despite all supportive measures.[113] EDB is postulated to lead to generation of free oxygen radicals through the cytochrome P450 pathway, which produces lipid peroxidation and membrane damage, resulting in hepatotoxicity and renal tubular necrosis. Dimercaprol has been suggested as an antidote based on the similarities in the structure of the 2 compounds.

CHROMIC ACID POISONING

Hexavalent chromium compounds such as chromic acid (H_2CrO_7) and its salts (chromates and bichromates) are used in the electroplating, leather tanning, and anticorrosive metal treatment industries. Renal lesions have been reported after acute ingestion of large quantities.[114,115] Ingestion is followed by severe abdominal pain, vomiting, gastrointestinal bleed, and circulatory collapse. Renal damage manifests as acute tubular necrosis (ATN). Dichromate is directly nephrotoxic and produces extensive proximal tubular necrosis. Hypotension and hemolysis also contribute to tubular damage. Management entails gastric lavage with alkaline solutions such as soda bicarbonate to prevent absorption and intravenous fluids to combat hypotension. Forced diuresis enhances renal excretion of the compound. Reducing agents such as vitamin C have been shown to prevent chromic acid–induced ATN in experimental animals.

HEAT STROKE

Heat stroke occurs when the body's thermal regulatory mechanism is unable to dissipate an adequate amount of heat, leading to an increase in body temperature. The exact incidence of heat stroke is not known; cases are observed in the summer months in tropical areas of Asia that have high ambient temperatures and relative humidity.[116,117] The condition affects mainly elderly individuals living in poorly ventilated places, but can develop in healthy adults after heavy physical exertion in a hot and humid environment.

The characteristic features are hyperpyrexia, hyperventilation, nausea, vomiting, cramps, ataxia, and incoherent speech, followed by loss of consciousness, hypotension, and circulatory collapse. As the syndrome progresses, disseminated intravascular coagulation and oliguric renal failure may develop. Laboratory data show hemoconcentration, hypernatremia, hypocalcemia, and increased transaminase levels, aldolase, and creatine phosphokinase. Hemolysis, myoglobinuria, and disseminated intravascular coagulation are seen in severe cases. Urinalysis reveals high specific gravity, proteinuria, red blood cells, and granular and erythrocyte casts. The presence of multiorgan failure indicates a poor prognosis. Hyperkalemia often is striking because of associated rhabdomyolysis. Some patients show high uric acid levels.[118]

The pathogenesis is multifactorial, with hypovolemia, hypotension, myoglobinuria, and disseminated intravascular coagulation contributing to AKI. In some cases, obstruction owing to precipitation of uric acid crystals has been shown to be the dominant abnormality.[118] Extreme hyperthermia may directly damage renal tubular cells. The pathology shows acute tubular necrosis.

Management consists of rapid cooling by any method with continuous monitoring of temperature. Rehydration should be instituted with care because the fluid requirement in most patients is not much. Exchange transfusion may improve survival.[116]

NATURAL DISASTERS

Large parts of Asia are prone to natural disasters such as earthquakes, landslides, tsunamis, and floods. AKI develops as a result of rhabdomyolysis in people trapped under rubble and debris, and is compounded by dehydration and metabolic acidosis. Some recent descriptions of AKI in major earthquakes have come from Iran, Turkey, and Kashmir.[119] A large number of patients with AKI remain undiagnosed because of a lack of laboratory facilities at the site. Prevention of AKI should form an important part of planning of disaster relief. Experience from the earlier-mentioned earthquakes suggests that early in situ evaluation and intervention wherever required dramatically reduced the incidence of AKI.[120]

GLOMERULONEPHRITIS

Various forms of rapidly progressive glomerulonephritis and postinfectious glomerulonephritis constitute about 10% of all cases of AKI.[121] It continues to be a significant cause of AKI, especially in the pediatric population. The other forms of rapidly progressive glomerulonephritides giving rise to AKI are similar to those seen in the temperate zone.

SURGICAL AKI

AKI as a result of surgery and trauma has increased from 11% of all cases of AKI in the 1960s to around 30% in the 1980s and 1990s in most Asian hospitals. Obstructive uropathy constitutes a major cause of surgical AKI in some parts of Asia.[87,122,123] The high incidence of nephrolithiasis probably is related to inherited metabolic disorders, dietary factors, and fluid losses. Faith in the efficacy of indigenous medicines in dissolving stones causes delay in surgical intervention and hastens the development of renal failure.

Primary hyperoxaluria, a rare inherited disease, normally presents with slowly progressive renal failure. However, there are reports from Asia of patients presenting with AKI, especially after a diarrheal illness. The presentation and diagnosis often is delayed, leading to poor outcomes.[124]

AKI is an important cause of death in victims of thermal and electrical burns.[125] Delayed presentation increases the likelihood of AKI and mortality.[126,127] A study showed improved outcomes in those who received early management.

OBSTETRIC AKI

Improvements in obstetric care have led to a virtual disappearance of pregnancy-related AKI from the developed world. The contribution of obstetric causes to the AKI population was as high as 22% to 25% in India until the 1980s. Studies from Indonesia and Thailand also reported obstetric causes in 15% to 30% of all cases of AKI. This high incidence was mostly because of unsafe home delivery practices in rural areas and clandestine abortions conducted by untrained personnel.[128] The abortion prac-

tices included the use of sticks; the insertion of abortifacient chemicals, pastes, and soap solutions; and dilatation and curettage performed under unhygienic conditions.[129] The incidence decreased to 5% to 8% after the legalization and regulation of abortions and the increased availability of medical facilities.[130,131] A similar experience has been reported from Turkey.[132]

The frequency distribution of AKI is bimodal in terms of duration of gestation.[129] The first peak, seen between 8 and 16 weeks, is associated chiefly with septic abortions and now is encountered less frequently. The second peak is after 34 weeks, and is related to pre-eclampsia, eclampsia, abruptio placentae, postpartum hemorrhage, and puerperal sepsis.[133-136] AKI develops owing to inadequate medical care at local health facilities and is unlikely to decrease until proper medical facilities reach the community.

AKI is oliguric in more than 85% of cases, and about a third of patients are anuric at presentation.[76,129] Other findings are jaundice, bleeding manifestations, seizures, and coma. The outcome of pregnancy-associated AKI is better than that of nonobstetric AKI. However, the mortality rate is high when the medical care is sought late and other organs have become involved.

Histology usually shows acute tubular necrosis. Acute cortical necrosis has been observed in more than 25% of patients in parts of India.[129] The dominant factor in patients developing AKI during pregnancy is renal ischemia caused by hemorrhagic shock or the hypotensive effect of overwhelming infection. Vasoactive phenomena and disseminated intravascular coagulation lead to vasoconstriction, resulting in cortical ischemia. This is accompanied by a striking decrease of renal blood flow. Swelling of the endothelial cells in patients with eclampsia contributes to the cortical hypoperfusion.

ACUTE CORTICAL NECROSIS

Acute renal cortical necrosis (ACN) is the most catastrophic of all types of AKI. It can develop after a variety of conditions, the most common being a complication of pregnancy[133] and snake bite. In a large series reported from India, obstetric causes were responsible in 56% of all cases of ACN. In some parts, the incidence has decreased in recent years.[137]

The most striking feature of this condition is a prolonged period of oliguria and anuria. This phase may extend for weeks to months, and patients with diffuse cortical necrosis may never enter a diuretic phase. Other findings depend on the underlying disease, severe blood loss, or fulminant sepsis being most prominent. Hypertension may be an early and prominent finding.

Renal recovery depends on the amount of viable cortical tissue, and can be slow and incomplete as the surviving nephrons hypertrophy to compensate for the lost mass. In our study, only 17% of patients could discontinue dialysis by the end of 3 months. The rest either died or remained dialysis-dependent. Kidney function deteriorates with time in patients who have achieved partial functional recovery. The longest recorded dialysis-free survival has been 12 years.[138]

The diagnosis should be suspected in all patients who show a prolonged period of oliguria and anuria. The gold standard for establishing the diagnosis is renal biopsy. In recent years, CT scan has emerged as a reliable noninvasive imaging modality for early diagnosis of acute cortical necrosis.[139,140] The characteristic findings include a lack of enhancement of renal cortex after contrast injection, medullary enhancement, and absent renal excretion. Cortical tram-track or egg-shell calcification develops later and may be detected on a plain radiograph, ultrasonography, or CT scan.

Histology shows a variable degree of necrosis of all elements of the renal parenchyma, especially the cortical region. Some cortical tissue in the subcapsular and juxtamedullary region may be spared and its hypertrophy is responsible for a partial recovery of renal function. Other findings include fibrin thrombi in the glomerular capillaries, fibrinoid necrosis of vessel walls, calcification of the necrotic areas, and cortical hemorrhages.[138] The lesion may be classified into patchy and diffuse types, depending on whether the entire parenchyma or only a part of the renal tissue examined showed features of acute cortical necrosis.[138] Needle biopsy can at best give only an approximate idea about the extent of the lesions and could underestimate

or overestimate the extent of lesions because of sampling errors.

The pathogenesis of ACN remains unclear. The main hypotheses are vasospasm of small vessels or toxic capillary endothelial damage. Prolonged vasospasm of both cortical and medullary vessels induces cortical necrosis in experimental animals. The reasons for propensity to renal cortical necrosis during pregnancy are not clear. Renal vasculature in pregnancy may be more prone to vasoconstriction secondary to the effect of sex hormones. Similarities between acute cortical necrosis and the generalized Schwartzmann phenomenon induced in experimental animals by injection of endotoxin also have been noted. In contrast to nonpregnant animals, in which 2 small doses administered 24 hours apart cause this phenomenon, only 1 injection is sufficient in pregnant rabbits. The presence of fibrin thrombi in the vasculature of patients with acute cortical necrosis has led to consideration of intravascular coagulation as the initial event. Recently, a role for endothelium-derived vasoactive substances in the genesis of acute cortical necrosis has been proposed.[138] We have shown increased endothelin-1 levels in women with pre-eclampsia, which could contribute to renal ischemia. A potential role of ET1 gene polymorphism has been suggested. However, more studies are needed to establish the exact role of endothelin in the pathogenesis of acute cortical necrosis.

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