Epidemiology of Acute Kidney Injury in Latin America

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Summary: There is little reliable information on the epidemiology of acute kidney injury (AKI) in Latin America. It is generally assumed that AKI in the developing world affects mainly young and previously healthy people, with an etiologic spectrum relying on particular socioeconomic and environmental conditions. Transmissible diseases such as leptospirosis, malaria, dengue, diarrhea, among others, are recognized as important causes of AKI in these areas. On the other hand, in large cities and university hospitals in Latin American, the AKI spectrum is similar to that seen in developed countries. Large studies are needed to improve our knowledge to design preventive strategies for this potentially lethal disease that affects all population subgroups, from the socially and economically vulnerable to the wealthy. In this article the available information regarding AKI epidemiology in Latin America is reviewed. Data obtained by the Latin American Acute Renal Failure Commission from the Latin American Society of Nephrology through surveys performed in 1997, 2000, and 2004 are reported. Finally, 3 particular medical conditions frequently associated with AKI in Latin America are reviewed.

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Acute kidney injury (AKI) is a frequent and devastating syndrome characterized by a sudden decline of renal function. The mortality rate associated with AKI varies according to the cause of the syndrome and the existence of comorbidities and complications, of which the most important is multiorgan dysfunction syndrome, frequently observed in the intensive care unit (ICU) setting. In-hospital mortality is about 20% to 40%,[1-3] increasing to 70% to 80% in more severe cases, such as those seen in the ICU.[4-7]

Acute renal failure, whose terminology recently has been revisited,[8] was described in the late 19th century,[9] but it was only studied in-depth after the appearance of the artificial kidney during Second World War. In contrast to the advances in the knowledge of the syndrome pathophysiology, the available information about AKI epidemiology is scarce, partial, and limited mainly to tertiary hospitals in the United States and Western Europe. Moreover, figures vary in different studies, despite the similarity of the studied population.[10] This fact can be explained by several factors, including the lack of a common AKI definition, making it difficult to compare studies,[11,12] the different settings in which AKI occurs (community, hospital, and ICU),[13,14] the wide differences in the demo-

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graphic characteristics of the patients (age, geographic, social, and economic conditions), the diversity of the epidemiologic indicators used (cases per 1,000 discharges, cases per million population, and cases per 100,000 population), among others.

In past years, there has been a growing interest in investigating the epidemiology of AKI. Figures reported in the literature are quite different. Feest et al[15] and McGregor et al,[16] using a very restrictive definition of AKI (serum creatinine level of ≥500 μmol/dL) found an incidence of 172 and 185 cases per million population per year, respectively. In the same year, Liaño et al[17] published the results of the ARF Madrid Study Group in which they found an incidence of AKI (defined by a serum creatinine level of ≥2 mg/dL) of 209 patients per million population. Stevens,[18] in England, reported an incidence of AKI (increase of serum creatinine level ≥300 μmol/dL) of 486 cases per million population. The influence of age as a risk factor for AKI was well established by Feest et al.[15] The incidence in patients aged 80 to 89 years was 949 cases per million population, whereas in younger patients (<50 y) the incidence was 17.1 cases per million population. Similar results were reported by McGregor et al.[16]

More recently, 3 studies based on large administrative databases from the United States were published,[19–21] the results of which should be interpreted cautiously. These studies were based on retrospective databases, designed for administrative purposes, in which patients with AKI were identified according to the International Classification of Diseases 9th revision coding system. In the Liangos et al[19] study, the frequency of AKI was 19.2 per 1,000 hospitalizations, which is similar to the incidence reported by Xue et al[21] (23.8 per 1,000 discharges), who also showed an 11% increase per year in the incidence of AKI during the 10-year study period. Interestingly, Waikar et al[20] also found an increasing incidence of AKI that was associated with a decrease in mortality rate. The incidence rate increased from 61 per 100,000 population in 1988 to 288 per 100,000 population in 2002, whereas the overall mortality rate decreased from 40.4% to 20.3% during the same period. Nevertheless, large, prospective, well-designed studies are needed to accurately establish the incidence of AKI.

Unfortunately, consistent and comprehensive data on AKI prevalence and incidence in the developing world are even scarcer. According to the available information, the etiologic spectrum of AKI in developing world populations might be similar or quite different to that reported in developed world countries, depending on the particular hospital country or city characteristics and on the presence of striking socioeconomic and environmental differences.[22–31] Poverty, illiteracy, and limited access to health resources, associated with exposure to infectious agents and animal venoms, make diarrheal disease, leptospirosis, dengue, snakebites, pregnancy complications, and septic abortion, among others, important causes of AKI in developing countries. In brief, AKI in developed countries usually occurs in aged and sicker patients who frequently have undergone invasive procedures or aggressive treatments. On the other hand, AKI in the developing world may occur in younger and previously healthy individuals, frequently owing to a single cause that depends on exposure to infectious agents or animal venoms and is associated with inadequate sanitary and nutritional conditions.

EPIDEMIOLOGY OF AKI IN LATIN AMERICA

Approximately 4 billion of the world's 6.4 billion people live in developing countries. Malnutrition, high demographic growth rates, limitations in urban infrastructure, prevalence of agriculture associated with a low industrialization level, high illiteracy rates, and low technology are all well-recognized indicators of underdevelopment in most of these countries.

Latin America is a subcontinent composed of 20 countries, with a wide diversity of cultures, languages, geography, and a profound and unacceptable difference in social and economic conditions of the population. The population of Latin America is about 539 million. The per capita income is estimated to be $3,600, with a large difference between countries and regions.[32] Although in Latin America the life expectancy is 70.9 years, it ranges from 53.1 to 79.3 years among countries. Health expenses

vary largely from $23.9 to $4,432.7 per person per year.[33] It is easy to understand that this context explains not only the particular epidemiologic profile of AKI in the area, when compared with the developed world, but also the variations observed from country to country in Latin America. Transmissible diseases such as malaria, cholera, leptospirosis, enterocolitis, dengue, and exposure to animal venoms are considered the foremost causes of AKI in small cities and in the countryside (more epidemiologic studies are needed to consistently support this assertion), whereas ischemic and nephrotoxic-induced renal injury are the most important AKI causes in large cities or university hospitals.[4]

The earliest epidemiologic study in Latin America was published by Lanari et al[34] from Argentina and was performed in a large tertiary hospital in Buenos Aires. This study reported some causes of AKI that were more frequent at that time, even in the developed world, such as septic abortion. Although the incidence of this condition has diminished in some of the most developed countries in the region, it remains a major cause of AKI in others, particularly in the economically disadvantaged population.

Burdmann et al,[35] from Brazil, reported the changing spectrum of AKI etiology over time within the same tertiary university hospital (Hospital das Clinicas, University of Sao Paulo Medical School). During 1957 to 1966 the most frequent causes of AKI were noncompatible transfusion and surgery, whereas from 1980 to 1982 nephrotoxicity was the leading cause, and, finally, in 1993, sepsis, hypotension, and cardiac failure were the main causes of AKI.

Vukusich et al,[36] from Chile, applying the same methodology as that used by the Latin American Acute Renal Failure (LAARF) Commission, which will be described later, performed a prospective study in 10 hospitals at Santiago during a period of 6 months. A total of 114 patients were included, representing an incidence of severe AKI of 1.03 cases per 1,000 hospital discharges. Sepsis was the main cause of AKI, followed by renal ischemia, surgery, and nephrotoxicity.

The Uruguayan Critical Care Nephrology Study Group performed a 2-week survey in 80% of ICUs in the country, and identified AKI in 66 of 723 patients. According to this study, the incidence of AKI was 91.2 patients per 1,000 admissions. Hypovolemia, sepsis, and nephrotoxins were the most frequent AKI causes. No transmissible disease was identified as a cause of AKI in this survey.[37]

In summary, the limited epidemiologic information available about AKI epidemiology in Latin America in large cities and university or tertiary hospitals showed a profile similar to that observed in the United States and Western Europe: sepsis, surgery (particularly cardiac and abdominal aortic surgery), solid organ transplantation, and contrast agents and drugs (antimicrobial agents, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, antiretroviral agents, calcineurin blockers, among others). However, the true epidemiologic spectrum of AKI in Latin America as a whole has not been established yet.

LAARF COMMISSION DATA

The LAARF Commission was founded in 1996 to improve the understanding of AKI in the region, particularly its epidemiology, to identify the infrastructure and human resources, and the treatment modalities and technology available in the region. Given the paucity of data and the importance of having reliable epidemiologic information to design preventive strategies to offer human and infrastructural resources in accordance with the actual needs, the LAARF Commission performed 3 surveys.

The first Latin American AKI survey was performed in 1997. All national Nephrology Societies that were members of the Latin American Society of Nephrology and Hypertension (SLANH) were invited to participate in the study. A predesigned, easy-to-answer questionnaire was sent to interested investigators. Only patients with AKI undergoing renal replacement therapies (RRT) were included to improve patient enrollment. Nevertheless, only 5 countries answered the questionnaire, providing data from 157 patients (Figs. 1 and 2). Four years later, the LAARF Commission repeated a similar survey with similar results. The information provided by these studies is relevant but cannot be considered fully representative of

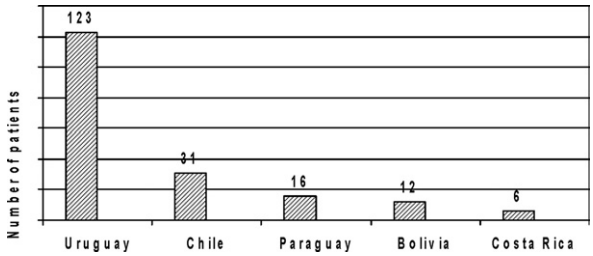

Figure 1. Results of the first Latin American survey of acute renal failure. A total of 157 patients were included in the study.

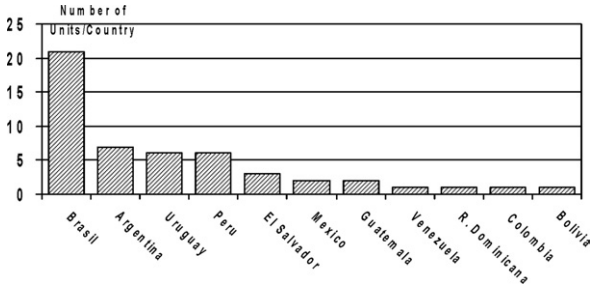

Figure 3. Distribution of units participating in the study, per country.

AKI epidemiology in Latin America because of the limited number of units participating in the survey, the majority located in large hospitals.

Given the scant information provided by these studies, the LAARF Commission organized another survey looking now at the quantity and qualification of the human resources available for the treatment of AKI patients, as well as the infrastructure available in the region for acute dialysis. The survey was performed in 2004. All acute dialysis units from Latin America were contacted and invited to participate in the study through the SLANH and by personal contacts. A web site of the LAARF Commission linked to the web page of SLANH (www.slanh.org/), containing a special form to be filled in with the information requested, was opened. Location and type of the unit, human resources (nephrologists, nurses), modality of RRT, dialysis machine, type of dialysate, use of treated water, number of procedures, number of patients treated, age, sex, number of patients in the ICU, and the global mortality rate were analyzed. Fifty-one units from 11 countries answered the questionnaire. In 19 of 51 questionnaires (37%) the information was complete. The remainder lacked information related to technology and/or patients. Fig. 3 shows the countries that participated in the survey as well as the number of units per country. The majority of units were located in the Department of Nephrology of teaching hospitals located in large cities (Table 1). All units had both nephrologists and registered nephrology nurses. The total number of nephrologists in the 51 acute dialysis units was 221, which represents 4 nephrologists per unit (range, 1-15). With regard to the available equipment, a total of 141 hemodialysis machines and 197 continuous renal replacement therapy (CRRT) devices were reported. The majority of CRRT devices were located in Brazil. As to the modalities of RRT that were available in the unit, all of them reported performing intermittent hemodialysis. Twenty-three units reported they also are capable of performing long, sustained dialysis and 29 units reported the use of CRRT. Of note, 34 units reported the use of acute peritoneal dialysis (PD). The dialysis membrane most frequently used was polysulfone, but 3 units still use cuprophane. In 7 of the 51 units, non-

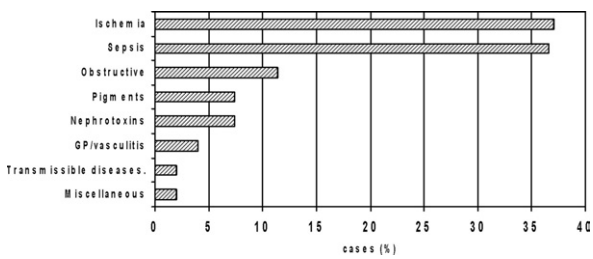

Figure 2. Etiology of the 157 cases of acute renal failure (values are expressed in percentages).

Table 1. Location of Units in Hospital Facilities and Type of Hospital

Location of units	
Department of Nephrology	26
Chronic dialysis units	11
ICU	10
Other	4
Type of hospital	
Teaching	58
Private	15
Public	8

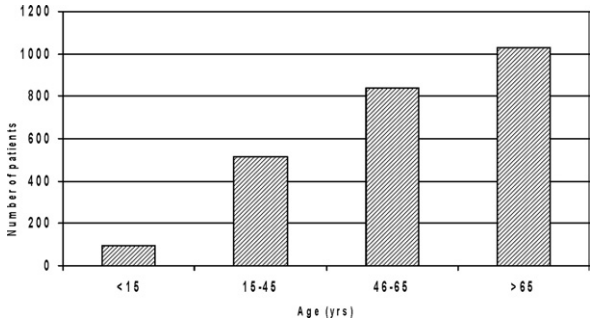

Figure 4. Distribution of patients according to age intervals.

treated water was used for dialysis. Data from 4,048 patients were reported. There was a wide variation in the number of patients per unit, ranging from 4 to 512. A total of 2,479 patients presented data about age and sex, resulting in a ratio of 61.8% males. Fig. 4 shows the distribution of the population by age intervals. Up to 63.8% patients were in the ICU. The overall mortality rate of the entire population was 32.3%. During the study period, information of 7,749 hemodialysis, 2,632 CRRT procedures, and 726 PD were provided. PD was performed in 10 units with a frequency ranging from 1 to 255 procedures during the study period. Of note, the 2 units that performed the highest number of PD were from Brazil (Sao Paulo and Porto Alegre).

The study had several weaknesses. First, it was not a fully representative sample of the unknown universe of acute dialysis units in Latin America. As expected, the rate of enrollment was low, considering the theoretically high number of acute dialysis facilities in this large region. Second, the sample probably was biased because the participants of the survey were nephrologists with some interest in the field working mainly in large teaching hospitals. Third, the reliability of the results could be impacted by the relative paucity of responses. However, some highlights can be pointed out. It contained information related to the organization, infrastructure, and modalities of RRT for patients with AKI in Latin America. According to the study, the units involved preferred intermittent hemodialysis, but it should be noted that there was a relatively high number of patients who were treated by continuous modalities, including PD as a frequent procedure.

In conclusion, the majority of hospitals participating in the study were teaching hospitals, which could have biased the results. There were still some units that use cuprophane membranes and do not have access to treated water. Patients showed a trend to old age and the mortality rate was relatively low, considering that this was a population of patients with severe AKI, frequently admitted to the ICU.

AKI AND LEPTOSPIROSIS

Leptospirosis, a zoonosis distributed worldwide, is caused by spirochetes belonging to the genus *Leptospira*. There are more than 200 pathogenic serovars of *Leptospira* and its prevalence occurs in humid tropical and subtropical areas, where most Latin American countries are located, making this infection a major public health burden, concerning human and veterinary medicine. Because of recent changes in meteorologic conditions with global warming, the World Health Organization has included leptospirosis as one of the re-emerging infectious diseases in both developed and developing areas.[38,39] Wild and domestic mammals are the usual vectors for leptospirosis (including rodents, dogs, pigs, cattle, horses, among others), which transmit the infection to human beings through their urine.

Human leptospirosis is endemic in Latin America and usually reaches epidemic levels after either higher rainfall periods with flooding, or natural disasters such as hurricanes.[40] Human cases range from 0.1 to 1 per 100,000 per year in temperate climates, to 10 to 100 per 100,000 per year in the humid tropics.[38,41] These figures increase during outbreaks and in high-risk groups. Epidemic leptospirosis was reported in Nicaragua in 1995[42] and 1998, when hurricane Mitch struck Central America.[43] In Puerto Rico, epidemic cases also were described after a hurricane in 1996[40] when dengue and leptospirosis diagnoses were mistaken. In Brazil, between 1985 and 1997, 35,403 cases were reported[44] and the mortality rate was 12.5%. In 1996, after summer floods in the city of Rio de Janeiro, 1,732 cases were described.[45]

Data from 1997 to 2006 showed similar figures: 33,043 cases with a fatality rate of 11.2%.[46]

Some studies showed a high seroprevalence of antibodies anti-*Leptospira* species in the general population. In Colombia, 18.4% of the studied population was positive.[47] In children ages 0 to 12 from Rio de Janeiro, the prevalence was 27.6%.[48] In Peru, 33.1% of the asymptomatic population was positive.[49] By using a polymerase chain reaction assay, 29% of wild small animals in the Peruvian Amazon were found to be infected by leptospiras.[50]

Renal involvement is almost universal in leptospirosis but becomes relevant in Weil's syndrome, which represents the most severe form of the disease, characterized by multiorgan involvement, and is associated with a high mortality rate (50%). The incidence of leptospirosis-induced AKI varies from less than 10% to more than 60% of infected patients.[41,51]

L. interrogans, the only parasitic species, is mobile, aerobic, and unstained by the Gram method. Its endotoxins affect the tubulointerstitial cells, and glomerular changes usually are not relevant. The bacteria's outer membrane contains lipopolysaccharide, which has no reaction on the Limulus amebocyte gelation activity test; glycolipoprotein, which is cytotoxic; and lipoproteins, especially lipoprotein 32, which causes immunologic effects and is a new hope for a universal leptospira human vaccine. Because leptospiras have special tropism for kidneys, the glycolipoprotein's effect on tubular Na,K–adenosine triphosphatase activity potentially is involved in both the leptospirosis-induced AKI cellular pathophysiology[52,53] and the paradoxic hypokalemia frequently seen in these patients.[54] High serum free fatty acids, mainly the oleic acid C18:1, also potentially are implicated in pulmonary hemorrhagic manifestations of acute respiratory distress syndrome associated with this disease.[55]

DENGUE FEVER

Dengue is an acute febrile disease, caused by an arbovirus, transmitted primarily by mosquitoes, with a benign evolution in most cases. It is the most important urban arboviral disease, affecting millions of people in all continents, except Europe. It is more prevalent in tropical and subtropical areas where the environment is favorable for the mosquito's development. The main dengue vector is the *Aedes aegypti* female mosquito. The male mosquito does not transmit the disease because they feed themselves with plant juices.

It is estimated that half the world's population lives in areas at risk for dengue disease and about 50 to 100 million cases are estimated to occur annually.[56–58] This disease is widespread all over Latin America, with few exceptions, such as Uruguay and some countries in the Bahamas area. From 2001 to 2006, more than 3.4 million people were affected in this area with 982 deaths. Sixty percent of dengue cases occur in the Latin America south cone. Brazil is the leading country in absolute number of cases and has one of the highest incidence rates of the disease in this geographic area, followed by the Andes region with 19%, where Colombia and Venezuela present most of the cases. However, there are currently more countries with high incidence rates, such as Costa Rica, Honduras, Bolivia, Chile, Paraguay, and French Guiana.[59–61]

Several factors account for the increasing incidence and spread of dengue in Latin America. Climate changes such as El Niño storms and global warming have influenced the intensity and duration of the rainy season and hurricane occurrences. These changes lead to ecosystem modifications, facilitating the expansion and dissemination of pathogens and vectors of the disease. In addition, demographic increases facilitating the occurrence of dengue in urban areas and in large cities, uncontrolled and unplanned urbanization, and migration of people are important factors in the increasing incidence and epidemics of dengue.[61]

There are 4 serotypes (DEN-1 to −4) of dengue RNA flavivirus. They are antigenically related but one serotype does not confer permanent immunity to another. All 4 dengue viruses are present throughout Latin America. The introduction of a new serotype accounts for the occurrence of epidemics and the hemorrhagic fever form of dengue that is more severe and may be lethal. In Brazil, in the 1990s, there were epidemics in a localized area with thousands of cases per year. However, in 2002 there

was a nationwide epidemic and endemic virus circulation, especially because of the introduction of a new serotype: DEN-3. From 1994 to 2002, a total of 2,826,948 cases of dengue were reported, giving an incidence of 454/100,000 inhabitants. The number of municipalities affected increased from 44.5% in 1996 to 58.3% in 2002. In 2006, there were 345,922 cases reported, especially in the southeast and northeast areas of Brazil. In that year, 682 hemorrhagic dengue fever cases were reported, with 121 deaths.[60-62]

Dengue virus infection may manifest as undifferentiated fever, dengue fever, dengue hemorrhagic fever, or dengue shock syndrome.[58] Usually, common clinical manifestations are high fever, myalgia and arthralgia, retro-ocular pain, headache, anorexia, nausea and vomiting, and a cutaneous rash similar to measles or rubella. Hemorrhagic/shock dengue fever have symptoms similar to the classic dengue fever associated with bleeding, abdominal pain, mental disorientation, sleepiness, breath shortness, tachycardia, shock, and death. Renal involvement includes proteinuria, glomerulonephritis, AKI, and hemolytic uremic syndrome. In dengue-induced AKI, renal failure usually occurs associated with shock, hemolysis, and/or rhabdomyolysis. However, dengue hemorrhagic fever–induced AKI without simultaneous occurrence of any other associated factors or drugs that may have caused renal failure recently was described.[63] There is no specific treatment for dengue fever. Therapy is mostly supportive, avoiding the use of aspirin and nonsteroidal anti-inflammatory drugs.

ANIMAL VENOM–INDUCED AKI IN LATIN AMERICA

Severe AKI has been reported after accidents with snakes, insects (bees and caterpillars), and spiders in Latin American countries. Currently, they represent a small percentage of AKI cases in many tertiary hospitals and in large cities, but animal venom may be an important cause of AKI in certain geographic areas or specific hospitals in Latin America. Moreover, this sort of AKI frequently occurs in young, previously healthy, and productive population members.

The large majority of animal venom–induced renal injury in Latin America is owing to snake poisoning from the *Bothrops* and *Crotalus* genus. AKI is considered the most serious and lethal complication of these accidents.[64] Renal injury develops a few hours after the bite, and may be oliguric, severe, and dialytic.[65] *Bothrops* snakes are responsible for around 80% to 90% of the reported venomous snakebites in Latin America. Retrospective studies have shown that AKI occurred in 1.5% to up to 10% of cases, but probably underestimated the real magnitude of this problem.[66-68] Renal histology usually discloses acute tubular necrosis, but some cases of acute cortical necrosis have been reported and glomerular injury was described in an experimental model.[65,69-71] *Crotalus* snakes are responsible for 7% to 8.5% of the total venomous snakebites reported annually in Brazil. AKI occurs frequently and a recent prospective study found an AKI prevalence of 29% after a *Crotalus* bite in Brazil.[72] Pathology discloses acute tubular necrosis, although acute interstitial nephritis was described in a few cases.[73,74]

Poisonous arthropods such as bees, caterpillars, and spiders also may induce AKI. Patients receiving hundreds of simultaneous bee stings frequently develop a complex clinical picture with intravascular hemolysis, rhabdomyolysis, hepatic injury, low platelet count, coagulopathy, bleeding, cardiovascular and pulmonary changes, and early development of AKI.[75,76] The increase and spreading of Africanized bees in Latin America dramatically increased the number of bee venom–induced AKI cases in the area in past years.[77] In experimental studies and in the few cases in which renal histology was available it showed acute tubular necrosis.[75,77] Accidents with caterpillars of the genus *Lonomia* produce severe hemorrhagic disorders. The venom has strong fibrinolytic action and enzymatic activities similar to tissue plasminogen activator, kallikrein, factor Xa, and urokinase.[78] The venom-induced hemorrhagic diathesis is complex, with both fibrinolytic and disseminated intravascular coagulation-like activity.[78] AKI has been reported after *Lonomia obliqua* accidents in Brazil.[79] *Lonomia* venom caused severe and prolonged AKI, with renal histology suggesting ischemic injury.[80] Spiders

of the genus *Loxosceles* may induce late local necrosis at the bite site, intravascular hemolysis, rhabdomyolysis, coagulation system changes, and acute renal injury. Even patients with a mild cutaneous lesion may present severe hemolysis and AKI, which is the main cause of death after theses accidents.[81–83]

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