Malarial Acute Kidney Injury: 25 Years Experience from a Center in an Endemic Region

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Authors’ contributions

This work was carried out in collaboration between all authors. Author RN designed the study, collected the data and wrote the manuscript. Authors FA, EA, RS, SB, AH helped in management of patients, author AN helped in arranging laboratory assessment generated funds and author AR being director of institution helped in overall arrangements towards patient care. All authors read and approved the final manuscript.

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ABSTRACT

Background: While malaria rarely occurs in many parts of the world, it still causes serious complications like acute kidney injury (AKI) in endemic areas and needs to be reported.

Methods: This study was carried out at Sindh Institute of Urology and Transplantation, Karachi, Pakistan. From January 1990 – December 2014, 5623 patients with acute kidney injury (AKI) were registered at this institution. AKI was defined as sudden rise in creatinine or decline in urine output or both. All patients had normal sized non obstructed kidneys on ultrasonography, with no previous co morbidity. Malaria parasite was seen on blood peripheral film in all patients.

Results: Among total patients with AKI, 671 (11.93%) developed AKI in association with malarial infection. Average age of patients was 33.70±16.426 (range 4-98 years) with M: F ratio of 3:1. The causes were plasmodium falciparum in 59%, vivax in 15.2%, dual infection in 3.57% and undefined.

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species in the rest. Oligo-anuria and vomiting were the most common associated symptoms along with fever. Renal replacement therapy was required in 76.6% of patients. Complete recovery was seen in 64.82%, while 21.2% died during the acute phase of illness. Jaundice, old age, altered level of consciousness, raised total leukocyte count, oliguria, hyperkalemia and falciparum malaria were the independent risk factors associated with high mortality.

**Conclusion:** Malaria still causes significant morbidity and mortality in our part of the world. Vivax malaria which was thought to be ‘benign’ can present with hemolysis, thrombocytopenia and kidney failure, though risk of death is 2.36 fold higher with falciparum malaria.

**Keywords:** AKI; malaria; P. falciparum; P. vivax; hyperkalemia; oliguria.

1. INTRODUCTION

Malaria is a serious parasitic infection, sometimes life-threatening, caused by one of the plasmodium species that are transmitted to humans through the bites of infected anopheles mosquitoes. According to World Health Organization (WHO) fact sheet no. 94, (published in March 2014), 207 million cases of malaria were reported globally in 2012 (range 135 to 287 million). According to the report, malaria caused an estimated 627 000 deaths (range 473 000 to 789 000), mostly among African children. In fact, the report stated that a child dies every minute from malaria in the African region [1].

Acute kidney injury (AKI) is one of the most dreaded complications of malaria. Acute kidney injury in malaria can mediate through several mechanisms. It may be due to the effect of parasitized red blood cells in circulation. According to studies, these red blood cells develop knob like structures on their surface, causing endothelial damage. Another problem that can arise is the adherence of red cells to each other and to vessel walls. These problems can result in affecting many organs [2,3].

Another complication is hypovolemic shock, which can result from hyperpyrexia, sweating, decreased fluid intake, vomiting, and in some cases, diarrhea. Vascular endothelial changes can also activate platelet adhesions, thrombocytopenia and disseminated intravascular coagulation. Inflammatory cytokines are found to be raised after malarial infection, including tumor necrosis factor (TNF)α, interferon (IFN)γ, interleukin (IL) 1,4,6,8, endothelial leukocyte adhesion molecules and intracellular adhesion molecules (ELAM 1, ICAM 1) [2,4,5]. There is evidence of vasoconstriction with release of certain chemical mediators like catecholamine and role of reactive oxygen species. Nitric oxide (NO) has also been reported with malarial infection. An increase in NO causes activation of T helper cells (Th1 and Th2) [2,6,7]. This series of events causes alterations in hemodynamics and consequently, there is compromised renal blood flow resulting in malarial AKI (MAKI).

There are many published reports on MAKI, both from tropical and non tropical regions. In the past, we have also published our experience of outcomes in patients with MAKI [8]. The current study reports 25 years of experience from a single tertiary care centre in treating patients with MAKI and studying outcomes.

2. PATIENTS AND METHODS

This study was carried out at Sindh Institute of Urology and Transplantation, Karachi, Pakistan, over a period of 25 years, i.e. from January 1990 to December 2014. Case records of all patients coming to this institute with AKI were reviewed and data was collected from patients who developed AKI in association with malaria infection. AKI was defined as sudden rise in serum creatinine (>2 mg/dl) in a previously healthy person, or decline in urine output (<400 ml/24 hours), or both.

If we consider the more recent classifications of AKI in medical literature, according to the RIFLE criteria, all of our patients fall in categories ranging from ‘Injury’ to ‘Loss.’ According to the AKIN classification, they fall in stages 2-3 [9]. Serum creatinine was checked by auto analyzer Hitachi 704 from 1990-1995 and later Beckman Coulter Synchron clinical system. Only patients with a recent history of malaria were included. The duration of illness when they came to the Institute ranged from 1 day to 1 month. Malaria was diagnosed through Giemsa stain or modified Leishman stained blood peripheral film. Immunochromatographic technique was used to diagnose malaria in patients who came to the Institute at a later stage, after having already
received some treatment at peripheral hospitals. Only patients with no past medical history were included and all patients had normal sized non obstructed kidneys on ultrasonography. Variables recorded for each patient on day of admission included age, history, duration of insult, oliguria, anuria, hemoglobin, total leukocyte count, platelet count, prothrombin time, activated partial thromboplastin time, blood peripheral film, blood urea, serum creatinine, serum sodium, serum potassium, venous bicarb, serum lactate dehydrogenase, serum bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, urine dipstick, urine microscopy, ultrasonography, parenteral fluids before renal replacement therapy, renal replacement therapy, sessions of hemodialysis or days on peritoneal dialysis, anti-malarial drugs given before coming to this hospital and outcome following treatment.

The institutional ethical review committee granted permission for publishing this data.

2.1 Statistical Methods

Quantitative variables are reported as means ± SD and qualitative as percentages. For univariate analysis of mortality risk factors Student’s t-test was applied. Categorical variables were summarized as frequencies and percentages and then analyzed by the Chi-square test or Fisher exact test where appropriate. Statistical analysis was done on SPSS version 19.0. Logistic regression was done by using STATA 14.0.

3. RESULTS

During the studied period 5623 patients with AKI were brought to this institution, among whom 671 (11.93%) had malarial AKI. The average age of patients was 33.70±16.42 years (range 4-98), with 510 males and 161 females.

In 59% patients the diagnosis was falciparum malaria, 15.2% had vivax infection, while 3.57% were infected by both species. In 22.2% patients, malaria was diagnosed at another hospital and patients were referred here because of renal dysfunction. In these cases, the species was not specified (Table 1). Vomiting and decline in urine output were common associated symptoms along with fever. Neurological involvement was found in one fourth of the patients (Table 2). Average patients had anemia, thrombocytopenia, and advanced uremia. 24% had high serum potassium levels and 34% had low sodium on presentation (Table 3).

| Species                      | Number of cases | %   |
|------------------------------|-----------------|-----|
| P. falciparum                | 396             | 59  |
| P. vivax                     | 102             | 15.2|
| Both falciparum & vivax      | 24              | 3.6 |
| Unknown (records reflect MP positive, species not specified) | 149 | 22.2 |

| Symptoms                      | Occurrence in percentages |
|------------------------------|---------------------------|
| Fever                        | 100                       |
| Oligo-anuria                 | 74.7                      |
| Vomiting                     | 76.8                      |
| Jaundice                     | 21.16                     |
| Diarrhea                     | 10.6                      |
| Altered level of consciousness| 24.6                      |
| Convulsions                  | 3.6                       |
| Dyspnoea/Breathlessness      | 11                        |

| Parameters                   | Values                    |
|------------------------------|---------------------------|
| Hemoglobin mean ± SD in g/dl | 8.72±2.78                 |
| Platelet count mean ± SD     | 138±146.96                |
| Blood Urea mean ± SD mg/l    | 318.413±413.87            |
| Serum Creatinine mean ± SD mg/l| 9.86±5.06              |
| Deranged INR (%)             | 21.16                     |
| Hyperkalemia K>5.5 meq/l(%)  | 24.3                      |
| Hyponatremia Na <130 meq/l(%)| 34.3                      |
| Microscopic hematuria (%)    | 52.8                      |
| Proteinuria 1-2+ on dipstick (%) | 38                  |

Renal replacement therapy was required on arrival in 76.6% cases and hemodialysis was carried out in all except 6 patients who received acute peritoneal dialysis. This was during the earlier period of the study when the hospital carried out peritoneal dialysis in small children and elderly patients. Complete renal recovery
was observed in 64.82% patients while partial recovery with no follow up was found in 14% patients. 21.2% patients died during the acute phase. Among those who died, 92 were male and 32 were females. The main cause of death was multi-organ involvement, that is, hepatic, nervous system, circulatory system, and respiratory system along with AKI.

With the application of logistic regression backward analysis, age, hyperkalemia, jaundice, altered level of consciousness, vomiting, higher total leukocyte count, presence of oligo-anuria and falciparum infection (in comparison to vivax) were found to be independent risk factors for mortality (Table 4).

## 4. DISCUSSION

In 1955, WHO declared that malaria would soon be eradicated from the globe. Ironically, WHO’s report for year 2012 (released in March 2014), reports 207 million globally infected cases with malarial infection. AKI was reported in 1-4.8% of falciparum malaria cases, [2] and contributed to <1 to 10.43% of the AKI population at different centers around the world [2,8,10,11]. However, the incidence of MAKI is reportedly much higher in some regions. A study from Thailand reports that 44% of patients with malaria developed acute kidney injury [12]. In our study, malaria contributed to 11.93% of total AKI. Significantly, this figure is higher than what was previously reported by the same institution [8]. It is a cause for concern that over the last five years we have seen an increase in the number of MAKI cases.

Pathogenesis of MAKI has several mediating mechanisms including endothelial damage, cytoadherance, cytokines up-regulation, vasoconstriction caused by mediators, hemolysis and disseminated intravascular coagulation [2,4-7,10-12]. Symptomatology from MAKI reports from different centers around the world indicate similar problems. Decline in urine output has been reported in 69-82 % MAKI cases [11,13]. In the present study, we found oliguria in 74.7% of patients, and also found that this was an independent risk factor of mortality. Liver dysfunction/ jaundice were reported in 21% patients in previous studies [2]. We have found a very similar pattern in our population. Cerebral involvement, which varies in reports from altered sensorium to coma, has been reported in 20-57% patients [2,13]. In our study, we have seen cerebral involvement in 24.6% patients, which is again in accordance with data from other studies. Jaundice and cerebral involvement were also found as independent risk factors for mortality in the present study (Table 4).

Hyponatremia is a typical biochemical finding in MAKI, being reported in up to 69% of cases with severe malaria [14]. There are various mechanisms reported causing this biochemical abnormality, including the syndrome of inappropriate anti diuretic hormone (SIADH) and cerebral salt wasting (CSW). However, in one study conducted at Oxford on samples from Bangladesh Hanson et al. [15] reported that ADH was released appropriately in response to hypovolemia.

Our study reports an inverse relationship of serum sodium levels with the level of consciousness, often with a fatal outcome. We found that those with a better level of consciousness tended to drink fluids to overcome hypovolemia and as mostly fluids taken are hypo-osmolar, this could give rise to hyponatremia. The shortcoming of the present study is that we could not measure fractional excretion of sodium (FeNa) in all patients. In some, this was not possible because of absolute anuria, while others had undergone dialysis elsewhere. In some case the excretion of sodium was not documented. Thus we are not in position to comment on renal handling of sodium in these cases from our own experience.

### Table 4. Independent risk factors for mortality

| Parameters                        | Odds increases by | Description                                      |
|-----------------------------------|-------------------|--------------------------------------------------|
| Age                               | 1.40%             | For every 1 year increase in age                  |
| Hyperkalemia (K >5.5meq/l)        | 64%               | For every 1 unit rise                             |
| Jaundice                          | 83.50%            | If present                                       |
| Altered level of consciousness    | 7.35 fold         | If present                                       |
| Vomiting                          | 2.07 fold         | If present                                       |
| TLC > 12000                       | 3.3%              | For every 100 rise in TLC                         |
| Oligo-anuria                      | 2.72 fold         | If present                                       |
| Falciparum malaria                | 2.36 fold         | As compared to vivax malaria                     |
Hyperkalemia is a striking feature of MAKI, and often fatal with its associated complication of cardiac arrhythmias. It is attributed to hemolysis, rhabdomyolysis, and acidosis, particularly in the setting of renal failure. One quarter of our studied population suffered from hyperkalemia and statistical analysis showed that it was a significant independent risk factor for mortality. Coagulopathy from previous studies has been reported in 5% of the population [2,12] whereas in the present study it was 21.16%.

In the past infection with plasmodium vivax was thought to be more benign than falciparum. However, this is no longer the case. Over the last two decades, we have seen this species causing a whole spectrum of pathogenesis quite similar to falciparum. However, in our study, mortality was higher in patients with falciparum as compared to those infected by vivax. In literature, hemolysis, disseminated intravascular coagulation (DIC), hypotension and hyperbilirubinemia from vivax malaria has been reported from India, in two case series of 19 and 40 cases [16,17].

Mortality in MAKI has been reported in 21-37.9% patients world over [8,12,18]. Our study shows a slight decrease in the mortality rate of our patients, i.e. 26% in the past [8] as compared to 21% in the present study. Previously, we have reported cerebral involvement and coagulopathy as poor prognostic factors in MAKI [19]. Others have also reported central nervous system involvement, DIC, sepsis, jaundice, anemia, hypotension and severe decline in urine output as poor prognostic factors [11,20]. In our present study, oligo-anuria, excessive vomiting, jaundice, high total leukocyte count and hyperkalemia were also noticed as independent risk factors for mortality.

5. LIMITATION OF STUDY

This study was carried out at a tertiary care unit where patients are referred from all over the country. Many of them reach here in advanced renal failure and thus require renal replacement soon after arrival. The incidence of malarial infection in the general population and the relative risk for malaria causing AKI thus cannot be calculated. Furthermore, many of the patients had received one or more antimalarial drugs before coming to this hospital and the contribution of drugs towards AKI cannot be commented upon.

6. CONCLUSION

Malaria still causes serious complications in endemic regions. In our experience, a remarkable number of AKI cases resulted from malarial infection, the majority being young patients. As part of the nephrology community, we have to learn to recognize risk factors for mortality related to MAKI and address them accordingly.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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