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# Contribution of Acute Renal Cortical Necrosis to Acute Kidney Injury: A 25-Year Experience from A Tertiary Care Renal Unit in Pakistan

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## Abstract:

Background: Acute cortical necrosis (ACN) is a rare contributing factor to acute kidney injury (AKI). The present study aims to report clinico-pathological profile and outcome of ACN in the setting of AKI.
Patients and Methods: This study was carried out at Sindh Institute of Urology and Transplantation, Karachi, Pakistan. Subjects for the study comprised a cohort of 349 patients, (6.2% of total AKI) seen over a period of 25 years. AKI was defined according to KDIGO guidelines and diagnosis of ACN was based on radiological or histological findings.
Results: From January 1990 to December 2014, 5,623 adult patients presented with AKI. Among these, 349 (6.2%) were found to have ACN. The mean age of ACN cohort was 29.33 ± 7.85 years. The major contributing cause was obstetrical AKI 286 (82%). On presentation 342 (98 %) were oligo-anuric. Histological diagnosis was available in 89 (25.50 %) cases, in 47 (53%) the pattern was diffuse and in 42 (47%) it was patchy. In rest, diagnosis was based on radiological findings. Hemodialysis was done in 346 (99.4 %). Complete recovery was seen in 9 (2.6 %), partial recovery in 76 (22%), chronic kidney disease (CKD) developed in 57 (16 %), end stage renal failure (ESRF) in 202 (58 %) while 5 (1.4 %) died during acute phase of illness.
Conclusion: ACN is still encountered as a cause of AKI. Some patients may remain dialysis free even with diffuse pattern on histological examination and this population should be closely monitored to avoid nephrotoxic exposure.

**Key Words:** Acute Kidney Injury (AKI), Acute Cortical necrosis (ACN), Pregnancy related AKI (PR-AKI), Snake Envenomation, Pakistan.

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## Introduction

Acute Cortical Necrosis (ACN) of kidney, which scarcely contributes to acute kidney injury (AKI), occurs as a result of markedly diminished renal arterial perfusion after vascular spasm, microvascular injury or intravascular coagulation and causes ischemic necrosis of renal cortex. ACN can be very extensive or diffuse or it could be focal or patchy. Renal medulla, juxtamedullary cortex and a thin rim of sub capsular cortex are mostly spared in these cases. The incidence of ACN is reportedly higher in developing countries than in the developed countries.[1] There are many etiological factors for ACN. Focusing on adult population, it may be related to snake bite, malaria, sepsis, trauma, shock, drugs and

poisons, burns, thrombotic microangiopathy (TMA), acute pancreatitis, antiphospholipid syndrome (APS), and the use of synthetic cannabinoids.[2-6]

In reproductive age females, it may result from septic abortions, abruptio placentae, post-partum hemorrhage,[7] prolonged intra uterine fetal demise, and severe eclampsia. More than 50% of ACN has been reported to be due to pregnancy related causes.[8]

Diagnosis of ACN previously was solely based on histopathological findings. Later on, radiological modalities like magnetic resonance imaging, computed tomography and ultra-sonography have become established modes of diagnosing ACN, where non-enhancing cortical rim is demonstrated that often correlates with the histopathological findings.[9,10]

The rationale of the study was to report the frequency of ACN among total cases of AKI among our patients presenting with AKI. The main objective of the study was to calculate the frequency of ACN cases in our patients and document its outcome as observed at a tertiary renal care unit in Pakistan.

## Patients and Methods

This is a retrospective, observational study involving data collection from case records, carried out at Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan over a period of 25 years, i.e. from January 1990 to December 2014. The study was approved vide Letter #SIUT-ERC-2020/A-216 dated August 10, 2020. This institute provides free-of-cost, life-long renal care to all patients coming for seek of treatment for any type of renal ailment. AKI was defined according to the KDIGO guidelines (criteria applied in retrospect),[11] as an increase in serum creatinine or decline in urine output.

ACN was defined on radiological findings of sonography as hypoechoic sub capsular cortical rim, or on computed tomography as a radiolucent zone bordering the circumference of both kidneys immediately adjacent to the renal capsule or histopathological findings of focal or diffuse/ extensive infarcted tissue in renal cortex.

Patients were labelled anuric when urine output was < 100 ml/24 hours and oliguric when it was < 400 ml/24 hours. Demographic data and laboratory parameters of patients included in study were recorded from the day of admission and these patients were followed up till they recovered normal renal function, or required renal replacement therapy (RRT) for long-term (specifically beyond 90 days), or dialysis free and long term follow up beyond 90 days (in some for decades) with abnormal serum creatinine/ GFR; this group was labelled as chronic kidney disease (CKD) according to KDIGO stages.[12] Some were lost to follow up before 90 days and were dialysis free; these were labelled as partially recovered. The study protocol is in accordance with the Declaration of Helsinki and Institutional Ethical Review Committee granted permission for publishing this data.

*Statistical Analysis:* Statistical analysis was done on SPSS version 22.0. Continuous variables were expressed as mean ± standard deviation, or median and minimum and maximum ranges were documented. Frequencies and percentages were computed for categorical variables.

## Results

During the study period from January 1990- December 2014, 5,623 adult patients with diagnosis of AKI were registered at this institution. Of these AKI patients, 349 (6.2%) were found to have ACN. Male: female ratio in this population was 1:22.26, as major contributing cause was pregnancy-related AKI. The baseline demographic, clinical and laboratory features are shown in Table 1 and the causes are tabulated in Table 2. Breakdown of obstetrical causes is given in Table 3. There were 266 (76%) patients who were anuric and another 76 (22%) oliguric on presentation. Renal replacement therapy (RRT) in the form of hemodialysis was started in 347 (99.4%) of these patients on arrival.

**Table 1.** Demographics and initial laboratory findings of the studied population (n=349).

| Parameters | Mean ± SD | Median | Range |
|---|---|---|---|
| Age (years) | 29.33 ± 7.85 | 28 | 18-70 |
| Duration of Insult (days) | 9.97 ±7.29 | 8 | 1-28 |
| Hemoglobin(G/dl) | 8.10 ±2.22 | 8 | 3-15 |
| WCC, $\times 10^3$ /µl | 18.94 ±9.17 | 17 | 2-68 |
| Platelets, $\times 10^3$ /µl | 226.69 ±174.47 | 179 | 7-1308 |
| Urea mg/dl | 181.77± 82.18 | 167 | 45-502 |
| Creatinine mg/dl | 10.34 ± 4.47 | 9 | 3-25 |
| Sodium mEq/L | 133.88 ±8.38 | 135 | 104-155 |
| Potassium mEq/L | 4.99 ±1.24 | 5 | 2-9 |
| Venous Bicarbonate mEq/L | 15.36 ± 4.96 | 15 | 4-29 |
| LDH U/L | 1866.55± 1905.52 | 1563 | 70-19360 |
| AST U/L | 140.05 ±398.68 | 44 | 3-3945 |
| ALT U/L | 107.99 ±248.75 | 34 | 2-2542 |
| Alkaline Phosphatase U/L | 160.18 ±128.30 | 126 | 34-1320 |

SD= standard deviation, WCC= white cell count, LDH= lactate dehydrogenase, AST= aspartate aminotransferase, ALT= alanine aminotransferase

Ultrasonography was performed on all patients: in 278 (80%), it was suggestive, while in 69 (20%) it was not suggestive of ACN, in 2 patients, CAN was diagnosed on CT scan (Figure 1). Renal biopsy was done in 89 (25.5%) patients, in 47 (53%), ACN was reported as diffuse and in 42 (47%), it was patchy (Figure 2).

A total of 9 (2.6%) patients gained complete recovery, 76 (22%) were in partial recovery phase till last follow up (dialysis free), while 57 (16%) developed CKD. The later remained on long-term follow-up in stages 2-4 of CKD, while 202 (58%) developed ESRF and required life-long RRT, (many proceeded for renal transplant), 5 (1.4%) patients died within 90 days and while still on RRT. Of 47 patients who were reported diffuse ACN on biopsy, 9 (19%) remained in CKD, 10 (21%) in partial recovery, 1 (2%) recovered completely and rest 27 (58%) developed ESRF.

## Discussion

ACN, focal or diffuse necrosis of renal cortex, results from intense vascular spasm and ischemia of renal cortex and includes necrosis of glomeruli and tubules. There occurs rapid decline in GFR and it is revealed by sharp decline in urine output. In present study, 76% of the studied population had anuria,

**Table 2.** Causes of acute cortical necrosis (N=349).

| Cause | Number of cases | % |
|---|---|---|
| Obstetrical | 286 | 81.9 |
| Snake Envenomation | 20 | 5.8 |
| Malaria<br>Vivax<br>Falciparum<br>Species unknown | <br>6<br>2<br>2 | 2.9 |
| Acute Gastroenteritis | 9 | 2.6 |
| Sepsis | 5 | 1.4 |
| Blood transfusion reaction | 5 | 1.4 |
| Poisons | 3 | 0.9 |
| Acute Pancreatitis | 1 | 0.3 |
| Acute Gastritis with GI Bleed | 1 | 0.3 |
| Appendicectomy (with no other co-morbid) | 1 | 0.3 |
| G6PD deficiency | 1 | 0.3 |
| Herbal Medicine | 1 | 0.3 |
| Meningitis | 1 | 0.3 |
| Unknown | 5 | 1.4 |

GI = gastro-intestinal, G6PD= glucose 6 phosphate dehydrogenase

**Table 3. Obstetrical causes contributing to acute cortical necrosis (n=286).**

| Causes | Number of patients | % |
|---|---|---|
| Abortion (septic) | 15 | 5.24 |
| Abruptio Placentae/ APH (isolated) | 6 | 2.09 |
| Abruptio Placentae/ APH + IUD | 25 | 8.74 |
| Abruptio Placentae/ APH + IUD+ LSCS | 5 | 1.74 |
| Abruptio Placentae/ APH + IUD+ LSCS + Sepsis | 20 | 6.99 |
| Abruptio Placentae/ APH + IUD+ LSCS + Post-Partum Hemorrhage | 10 | 3.49 |
| APH+IUD+PPH | 6 | 2.09 |
| APH+IUD+PPH+Sepsis | 30 | 10.48 |
| APH+ LSCS | 6 | 2.09 |
| APH+PPH | 6 | 2.09 |
| APH+IUD+Eclampsia | 8 | 2.79 |
| HELLP | 1 | 0.34 |
| HUS | 6 | 2.09 |
| IUD (isolated) | 9 | 3.14 |
| IUD+PPH | 33 | 11.53 |
| LSCS (isolated) | 10 | 3.49 |
| LSCS+PPH | 12 | 4.19 |
| P. Sepsis (isolated) | 3 | 1.04 |
| PET+APH+IUD | 37 | 12.93 |
| PPH | 34 | 11.88 |
| Ruptured Ectopic | 1 | 0.34 |
| Ruptured Uterus | 1 | 0.34 |
| Normal vaginal delivery at full term with no significant history | 2 | 0.69 |

APH= antepartum hemorrhage, IUD= intra uterine death of fetus, LSCS= lower segment caesarean section, PET= pre-eclampsia, HUS= hemolytic uremic syndrome, HELLP= hemolysis elevated liver enzymes and low platelet, PPH= post-partum hemorrhage

mostly absolute anuria and another 21% having oliguria, indicating the severity of insult to the kidneys.

ACN was reported in 33% of pregnancy-related AKI (PR-AKI) in 1980 in a French study.[13] Same group reported decline in cases of ACN in a later study.[14]
A study published from Pakistan reported ACN in 2.9 % of all renal biopsies over a period of 11 years and in all cases ACN resulted from PR-AKI.[15] From our institution, when biopsy pattern in AKI was analyzed, ACN contributed to 22.7% of all renal biopsies during a span of seven years.[16]

An Indian study has reported declining trends in ACN as a reflection of improving obstetrical care.[17] We have not previously published solely on ACN and causes contributing to it. So, this is first study from our institution addressing this subject in detail. We have found other than obstetrical causes contributing to this finding, although number of other causes is small and ratio of PR-AKI to other causes AKI in this studied population is 4.5:1. This is different from what is reported by Sahay et al in their study from India, where PR-AKI contributed 39.04 % to all causes of ACN.[18] Another study from Eastern India also reported PR-AKI contributing to 56.2% of total ACN.[8]

ACN after snake envenomation has been reported in literature specially from studies published from tropical region. This can result from direct toxic effects, shock and/ or hemorrhages.[19,20] We have also published from our institution the detailed account of mechanisms of AKI in some patients developing ACN in this scenario.[20] Present series shows that 6% of total population was contributed by snake envenomation.

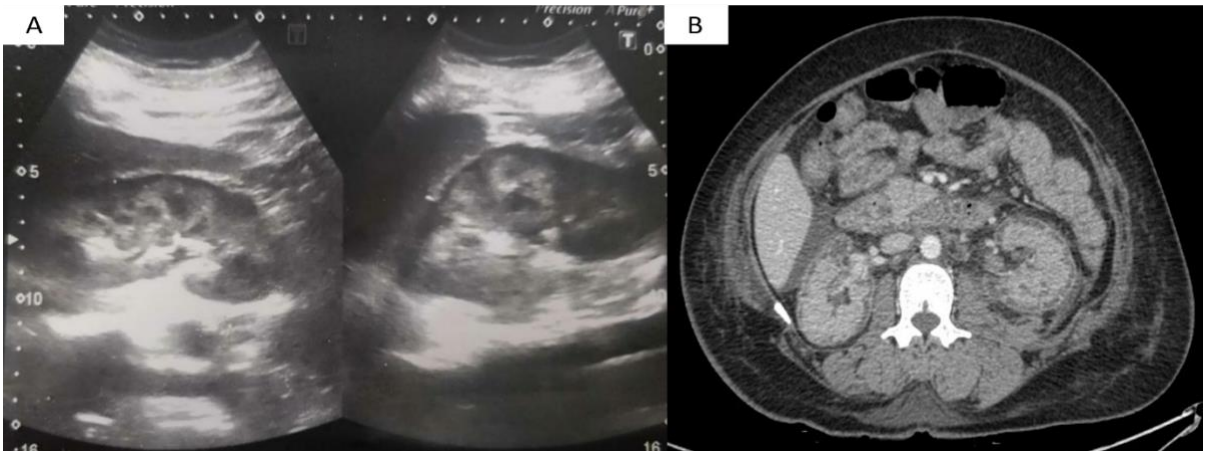


**Figure. 1**. Radiological findings in acute cortical necrosis. A- Ultrasound both kidneys showing hypoechoic peripheral rim. However, there is preserved cortico-medullary distinction. B- CT scan: Post contrast: Axial view: There is a non-enhancing renal cortex (yellow arrow) and a normal enhancing renal medulla which is called reverse rim sign. A very thin rim of contrast enhancement (cortical rim sign) is also seen (blue arrow). These findings are present in bilateral symmetrical pattern.

Malaria, both Falciparum and Vivax, has been reported to cause ACN[2,21-23] In our experience we have also seen and reported ACN with both species of malarial parasite.[2,23] In the present study, 6 patients developed AKI after Vivax malaria, two had Falciparum and two arrived late after getting malaria treatment at local facilities. They had reports mentioning malarial parasite seen on peripheral film but species of parasite was not documented. These patients when showed delayed recovery proceeded for biopsy or repeat sonography and found to have ACN.

Septic shock can be induced with Escherichia coli endotoxin (LPS) and can stimulate nitric oxide production, and ACN has been reported in such patients.[5] Other bacterial infections like streptococci have also been reported to cause ACN.[24]

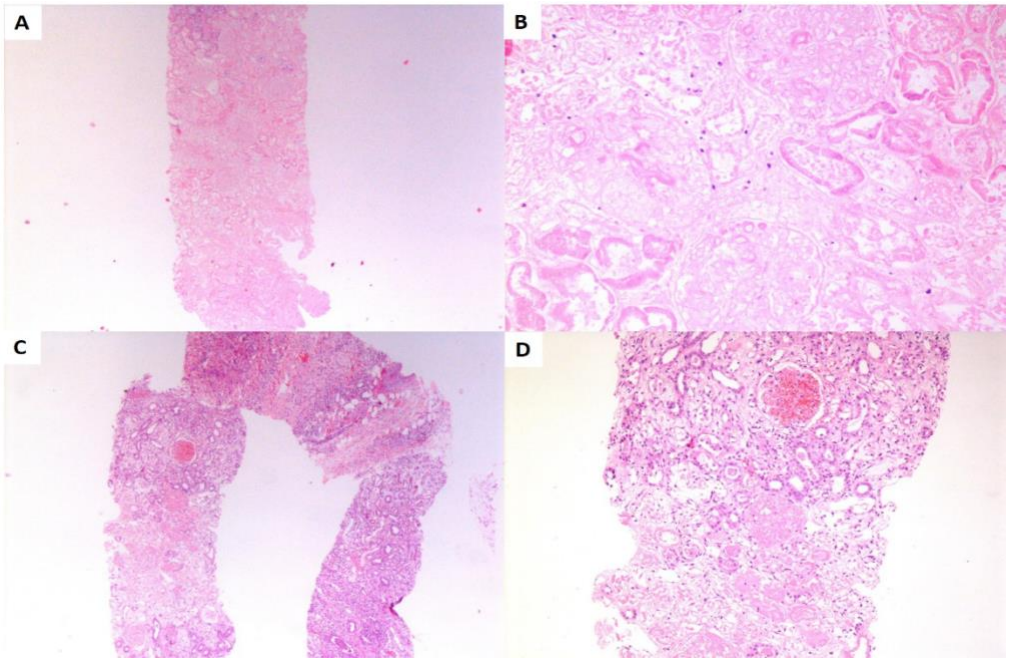


**Figure. 2**. Histopathology of acute cortical necrosis. A. Low-power view showing part of renal cortex showing complete infarction. No viable structures are seen. This qualifies for complete or diffuse cortical infarction (H&E stain, ×40). B. Medium-power view showing two glomeruli, both of which are infarcted. The surrounding tubules are also infarcted. (H&E stain, ×200). C. Low-power view showing patchy areas of cortical infarction along with some viable structures in a case of patchy cortical infarction. (H&E stain, ×40). D. Medium-power view showing two glomeruli, one of which (lower) is infarcted, while the upper glomerulus along with surrounding tubules is still viable but congested. (H&E stain, ×100).

In the current study, five patients had sepsis as cause for ACN. Of these, two had elective abdominal surgeries, another two had intra-abdominal sepsis without any intervention and one had uro-sepsis. Severe bacterial meningitis may rarely lead to AKI and/or rhabdomyolysis. Persistent renal failure should lead to the suspicion of bilateral renal cortical necrosis.[25] In present series, we had one patient presenting with AKI after developing meningitis.

Some toxins have been reported to cause ACN. These include organophosphorus compounds, heavy metals, glycol and some plant toxins.[24] In our studied population, three patients were exposed to

poisonous substances, two to more than one substance and one had paraphenylamine diamine (PPD) and came with toxic rhabdomyolysis and AKI. Renal biopsy in this patient was done because of delayed recovery. As our experience with PPD describes renal recovery within an average of 6 weeks.[26]

A study reported that only 18% of patients with ACN of the kidneys recover without long-term dialysis.[27] In present study, 58% developed ESRF requiring life-long RRT. But surprising feature was complete renal recovery in 9 (2.6%) patients, which was sustained on long-term follow-up. Also 133 (38%) patients remained dialysis free, and in many patients follow-up duration was more than a decade. This is important observation in terms of patient counselling that once diagnosed with ACN on ultrasonography or even on biopsy, should not lose hope and should be kept under strict avoidance for nephrotoxins.

Another interesting aspect of this study was that among 47 patients reported as diffuse or extensive cortical necrosis, 38 did not have suggestive ultrasonography and among 42, who were reported as focal or patchy cortical necrosis, 32 had non-suggestive ultrasonography. There were 19 patients who were reported on ultrasound as suggestive of ACN but biopsy was still performed. These were cases either from early years of study or history/ clinical presentation not supporting the findings of ultrasonography.

## Conclusion

In our experience, PR-AKI was the main contributing factor for ACN. ACN has poor renal outcome, but some patients can remain dialysis free and still few can recover normal renal functions. This was observed even when renal histology showed diffuse or extensive infarcts. Therefore, meticulous choice in prescribing antibiotics, analgesics or other known nephrotoxic drugs should be made.

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