

# Review Article

## Acute Renal Failure in children with Diabetic ketoacidosis

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### Abstract

Acute renal failure is an uncommon complication among children with Diabetic keto acidosis. This has been recently reported from developing countries. Prerenal uremia which improves in few hours is common in DKA and this is fluid responsive, however intrinsic renal failure with increasing urea creatinine and anuria is associated with high mortality and is uncommon. Sepsis, shock, severe dehydration, rhabdomyolysis and thrombotic microangiopathic syndrome are the underlying factors for acute renal failure in children with DKA. The incidence of acute renal failure varies from 3.7% to 11.5%. Management includes change in fluid electrolyte therapy, insulin dose, bicarbonate infusion and renal replacement therapy in the form of hemodialysis or peritoneal dialysis. Mortality in acute renal failure in DKA varies from 40 - 72%. Earlier identification of renal failure is mandatory for a better outcome.

**Key Words:** Acute renal failure, DKA, Children, Prognosis.

### Introduction

Diabetic keto acidosis(DKA) is a common metabolic disorder in children with Type 1 diabetes mellitus which has a mortality of 11% - 13.4% in developing countries.<sup>1,5</sup> Cerebral edema, sepsis, shock and renal failure contribute to the high mortality in DKA. Renal failure in children with DKA is mostly seen in developing countries. Literature from developed countries mention acute renal failure as a rare complication in children with hyperglycemic hyperosmolar state.<sup>6</sup> Renal failure in DKA due to rhabdomyolysis has been rarely reported to be a potentially lethal complication in children. Other factors associated with renal failure in DKA include sepsis, shock, severe dehydration and thrombotic microangiopathic syndrome. Early identification and management of renal failure may help improve the prognosis in DKA. This article is a mini review of available literature on the etiology and outcome of children with acute renal failure complicating DKA.

DKA is a metabolic derangement with varied degrees of fluid loss, at times presenting with hypotension and shock. However, rehydration in DKA is gradually carried out to prevent cerebral edema. Unique problems arise in DKA if complicated by sepsis or shock. Existing septic shock guidelines do not mention about specific fluid management for sepsis complicating DKA. Whether too much of fluids lead to cerebral edema or too less of fluids lead to renal failure is not addressed in literature. It is universal to have children with DKA presenting with elevated urea

creatinine at hospitalization. Renal function in DKA could be altered in two ways, one in which initially impaired renal function quickly returned to normal with correction of dehydration and this is commonly encountered in DKA. The other is where renal function continue to deteriorate for a variable period probably due to reversible renal ischemia. Dehydration related prerenal uremia is common in DKA. Pseudo hypercreatininemia is due to acetone interference in the laboratory evaluation in DKA.<sup>7-10</sup> However renal failure is uncommon in DKA due to the osmotic effect of hyperglycemia which tend to preserve the intra vascular volume despite diuresis. Diagnosis of renal failure in children with DKA is as per RIFLE criteria.<sup>11,12</sup>

Literature review revealed a few case reports and publications on renal failure in children with DKA which reveal the incidence to be 3.7 to 11.5%. Intrinsic renal failure in DKA is reported to occur in 11.5% of children from South India.<sup>13-16</sup> Case fatality reports vary from 40% to 72% in intrinsic renal failure complicating DKA.<sup>5,13</sup> Renal failure has been identified to be a significant risk factor for mortality in DKA by multivariate analysis in studies from south India and elsewhere.<sup>5,17,18</sup> Sepsis and shock were the common predisposing factors reported from south India.<sup>5</sup> Literature on renal failure in children with DKA is scarce and limited to few case reports.

Etiology of acute renal failure in DKA is multifactorial. Hypovolemia and hypotension are major contributory factors. Renal failure due to micro vascular involvement occurs in adults and that is not discussed in this article.

Pre renal hypovolemia, sepsis, shock, severe dehydration, rhabdomyolysis and thrombocytopenia related multi organ failure are some of the factors for acute renal failure in DKA. Children with monogenic diabetes (diabetes caused by single gene mutation) can have renal involvement as a part of the disorder. Sepsis has been increasingly reported to be a major predisposing factor for DKA in children with established diabetes as well as new onset diabetes. A high degree of suspicion is essential in DKA as these children rarely present with fever. Based on the published reports from developing countries occurrence of sepsis in DKA is much higher. Antibiotics may be started based on clinical suspicion until associated infection is ruled out in DKA.<sup>5</sup> Fever, shock refractory to fluids more than 30 ml/kg for resuscitation, persistent acidosis, anion gap more than 35 at presentation should make one suspect infection in the absence of an obvious focus in DKA at presentation.

Shock with acute renal failure is not uncommon in DKA from developing countries.<sup>2,3,5</sup> Fluid therapy in refractory shock needs to be studied in children from developing countries as the controversy still exists whether too much of fluids or too little of fluids is more harmful in DKA. Higher rate of fluid administration during resuscitation has been associated with cerebral edema and lesser fluids may predispose for hypovolemia related renal failure. Restriction of fluids for resuscitation may be more harmful in comparison to more fluids in children with refractory shock. Recent literature from India and elsewhere have not identified higher rate of fluid administration during resuscitation for shock in DKA to be a risk factor for death or cerebral edema.<sup>5,19,20</sup> Both cerebral edema and renal failure are associated with high mortality. Cerebral edema in children with DKA from developing countries is associated with a mortality rate of 50% and renal failure has the highest mortality of 72 % in a recent study from South India.<sup>5</sup>

There is an urgent need to study fluid therapy in children with DKA from developing countries as to give more fluids or less fluids in hypotension and shock complicating DKA. Hence the protocols for fluids based on guidelines from developed countries need to be reassessed for the suitability in developing countries with different problems complicating DKA in children.<sup>5</sup> Severe dehydration and shock may be a consequence of missed/delayed diagnosis and delay in establishing specific treatment. Missing the diagnosis of DKA is not an uncommon problem in children with diabetes from developing countries.<sup>21-23</sup> Missed / delayed diagnosis of DKA is due to lack of awareness among the parents and physicians. Delay in establishing specific treatment could be due to lack of availability of structured diabetic care teams for appropriate management of DKA. Creating awareness among physicians and parents to avoid delay and thereby hypotension and shock is mandatory.

Rhabdomyolysis as a cause for renal failure in children with DKA has been reported in the literature.<sup>24-27</sup> Hypokalemia and hypophosphatemia have been reported to be contributing factors for rhabdomyolysis.

Hypophosphatemia induced decrease of <sup>2,3</sup> DPG may affect the oxygen dissociation curve and thereby the oxygen delivery to tissues. Hypokalemia is also known to predispose to membrane instability and there by contribute to rhabdomyolysis.<sup>24</sup> This could be due to impaired energy to the muscle, hyperosmolarity and underlying metabolic derangements. A case series on rhabdomyolysis among adolescent diabetic patients had demonstrated rhabdomyolysis with renal failure.<sup>28</sup> Preformed creatinine gets released into the circulation causing elevation of creatinine levels disproportionate to urea in these children. Tubular damage in rhabdomyolysis is due to ferriheme toxicity, tubular obstruction by precipitation of myoglobin casts, alterations in glomerular filtration rate, myoglobin toxicity, hypotension, crystal formation and protease release from the muscles. Renal vasoconstriction and lipid peroxidation injury can lead to renal failure in rhabdomyolysis. Early recognition, adequate hydration and early hemodialysis are useful as therapy.

Thrombocytopenia associated multi organ failure (TAMOF) has been reported in children with DKA associated renal failure.<sup>29-33</sup> This is a thrombotic microangiopathic syndrome with thrombotic thrombocytopenic purpura (TTP), secondary microangiopathy (TMA) or disseminated intravascular coagulation (DIC). Renal failure alone in DKA would not suffice for a diagnosis of TAMOF/TTP. TTP is a pentad of symptoms that include thrombocytopenia, renal failure, seizure / abnormal CNS condition, microangiopathic anemia along with fever. Its pathophysiology has been ascribed to a decreased ADAMTS 13 activity (A Disintegrin And Metalloprotease with Thrombo Spondin motifs; formerly known as von Willebrand factor cleaving-protease) which results in large von Willibrand factor multimers leading to a massive platelet thrombosis in multiple organs, especially brain and kidneys. Typically, these patients have less than 10% of normal ADAMTS 13 activity. Non-consumptive secondary thrombotic microangiopathy is distinguished from thrombotic thrombocytopenic purpura by the absence or slight evidence of hemolysis on peripheral smear. Moreover, the ADAMTS 13 activity is moderately low (10-57%) as compared to thrombotic thrombocytopenic purpura (<5%). Endocrine cause of TAMOF /TTP is rarely reported in literature. Thrombotic microangiopathic syndrome associated with DKA may well be an under reported entity.

The cause of renal failure in hyperglycemic crisis is assumed to be "pre-renal" in majority of children. Kidney hypoperfusion results from hypovolemia due to osmotic polyuria and sometimes gastrointestinal losses. Majority of the children with acute kidney injury (AKI) show improvement of the renal parameters and normalize in 24-48 hours. The impaired renal function that normalizes with fluid administration is termed volume responsive AKI. This fits into majority of the children with DKA as they have elevated renal parameters at admission. Persistent azotemia with or without oliguria signifies a serious problem in DKA. In general AKI is considered as an independent risk factor for mortality in critically ill patients. Various

laboratory parameters to differentiate prerenal and intrinsic renal failure are difficult to interpret in DKA as the child receives normal saline in large volumes by the time renal parameters are available.

Presence of intrinsic renal failure in DKA necessitates modifications in fluid and electrolyte therapy. There are no standard guidelines for management of renal failure in DKA in children. Based on the existing literature fluid restriction, use of potassium free fluid, use of bicarbonate, intra venous fluid with lesser sodium content lesser insulin doses and renal replacement therapy in the form of peritoneal dialysis, hemodialysis and plasmapheresis are recommended for renal failure in DKA. Renal failure do need modification of the antibiotics used in case of sepsis complicating DKA. At the authors unit intrinsic renal failure is managed by fluid restriction according to the urine output. Potassium free fluid is continued till renal failure abates. Dosages of antibiotics are modified accordingly. Insulin doses are usually at 0.05 units / kg / hr or less and is titrated according to the blood glucose values. Children refractory to conventional treatment will undergo peritoneal dialysis. These protocols for management of renal failure in DKA are based on individual intensive care units and there is a need for uniform consensus on these management protocols. Use of fluid with less sodium content and use of bicarbonate in DKA always carry the risk of cerebral edema, which is a life threatening complication in DKA. However altered sensorium in DKA is multifactorial as it could be due to shock, renal failure, severe dehydration and cerebral edema. Individual contribution to altered sensorium by these factors is difficult to identify. Child on peritoneal dialysis for renal failure present with greater fluctuations in the blood glucose varying with the phases of dialysis. The altered insulin dynamics due to renal failure makes these children at high risk for hypoglycemia. Majority of these children need less doses of insulin infusion to maintain euglycemia sometimes with dextrose content of up to 12.5 % concentration to maintain euglycemia with persistent acidosis. Renal replacement therapy in the form of peritoneal dialysis has been used in children with renal failure.<sup>13,34</sup> Hemodialysis may be preferred in rhabdomyolysis and plasmapheresis has been found to be useful in thrombocytopenia associated multiorgan failure.<sup>29,30</sup>

A child with DKA and shock or severe dehydration where the blood glucose does not fall with adequate fluids and appropriate insulin infusion should raise an alarm for suspecting renal failure. This will soon be followed by persistent acidosis, increasing urea creatinine and rapidly declining blood glucose in few hours despite increasing dextrose containing fluids in DKA. An initial elevated urea creatinine is more common as dehydration is a part of DKA. A combination of wide anion and non anion gap acidosis may be a clue for evolving renal failure. Failure of urea creatinine to fall with fluid and insulin therapy will be the other supporting evidence for intrinsic renal failure. Non oliguric renal failure is much more common in DKA in the initial phases and once hyperglycemia is controlled oliguria may set in.<sup>13</sup>

This persistent acidosis restrains one from switching over from insulin infusion to subcutaneous insulin therapy.

Reduction in mortality is feasible by prevention and earlier intervention for renal failure. There is an urgent need for standard treatment protocols for management of this uncommon yet a life threatening or fatal complication of DKA in developing countries.

### Points to remember

Acute renal failure though uncommon in children with DKA has a high mortality rate.

Sepsis, shock, severe dehydration, are the common factors contributing for acute renal failure in DKA. Rhabdomyolysis and TAMOF are rare causes.

Modification in fluid therapy, use of bicarbonate, lower doses of insulin, modification in the dose of antibiotics and renal replacement therapy are the management strategies to be followed in Renal failure in DKA.

There is an urgent need for standard treatment protocols for management of renal failure in DKA in children.

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