# Living with Distal Renal Tubular Acidosis: Qualitative Research with Nephrologists, Patients, and Caregivers

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# Abstract

**Rationale & Objective:** Clinical consequences of distal renal tubular acidosis (dRTA) may include profound dehydration, failure to thrive, growth delay, rickets, hearing impairment/loss, nephrocalcinosis, and nephrolithiasis. Little has been published about patients' and caregivers' lived experiences with this rare disease. This study provides context and understanding of patients' and caregivers' perspectives as well as the nephrologists' experiences managing the patient with dRTA.

**Study Design:** Descriptive qualitative study.

**Setting & Participants:** One-on-one, semi-structured, one-hour telephone/WebEx interviews were performed using an interview guide. Four pediatric nephrologists experienced in the treatment of dRTA, two adult patients, a pediatric patient and caregiver pair, and one caregiver of a pediatric patient participated from the United States.

**Analytical Approach:** Thematic analysis of interview transcripts was conducted utilizing a qualitative data analysis software.

**Results**: Three primary themes emerged from the analysis of the interviews: diagnostic challenges, burden of disease, and burden of treatment. Nephrologists provided complete insights into the diagnostic and clinical challenges associated with dRTA and its management, including previous misdiagnosis, and poor adherence to medication regimen. Patients and caregivers added to understanding the significant physical, social, emotional, educational/professional, and health-related quality of life (HRQoL) impacts of the disease. Patients, caregivers, and nephrologists were aligned on the significant unmet needs associated with current medicinal standard of care (SoC) due to high dosing frequency, low palatability, and tolerability of available treatments.

**Limitations:** Due to rare disease recruitment challenges, the sample size was small and lacked geographic diversity.

**Conclusion:** Interview findings bridge the gap in knowledge regarding patient and caregiver lived experience with dRTA and support the need for increased recognition of the disease and the use of algorithms to improve the diagnostic challenges. Key findings included frequent alkali dosing is a barrier to medication adherence and the need for improved social/emotional support for patients and caregivers.


# Introduction

Distal renal tubular acidosis (dRTA) is a rare disorder with an estimated prevalence of 0.38 per 100,000 in the 2016 US employer-sponsored insurance population[1], and 0.46 to 1.6 per 10,000 individuals in the United Kingdom.[2]

Distal RTA should be suspected when children present with hyperchloremic, hypokalemic metabolic acidosis in the presence of a normal plasma anion gap and a urinary pH > 5.5.[3] Clinical consequences of dRTA include profound dehydration, failure to thrive, growth delay, rickets, nephrocalcinosis, nephrolithiasis, and associated decreased renal function. In addition, muscle fatigue, cramps and cardiac arrhythmias can be seen with hypokalemia.[4] A recent study conducted among European nephrologists who reported information on 340 patients with primary dRTA highlighted an increase in chronic kidney disease Stage ≥ 2 in children (35%) and adults (82%).[5] Hearing impairment may also be present in certain hereditary dRTA forms (e.g., *ATP6V1B1* and *ATP6V0A4* variants).[4,6]

Current standard of care (SoC) treatments for dRTA present limitations as medication regimens are usually administered every four to six hours, have poor palatability and gastrointestinal (GI) tolerability, leading to adherence challenges and render adequate metabolic control challenging.[7] Adequate metabolic control (i.e., normal plasma bicarbonate and urinary calcium excretion levels) associated with improved growth and renal function was achieved in only 51% of patients in the aforementioned European study.[5] Recent research has progressed our understanding of underlying physiological causes of dRTA and long-term clinical outcomes.[8,9] However, little is published about the diagnostic odyssey of patients and caregivers; lived experiences with dRTA burden of disease; impact on physical, social, and emotional functioning; impact on health-related quality of life (HRQoL); and the unmet needs associated with current SoC.

The aim of this descriptive qualitative study was to increase the understanding of the dRTA lived experience, including context obtained through the experiences of nephrologists managing patients with dRTA, in order to provide insight of the impacts on patients, caregivers and other family members, and on the potential limitations of current SoC treatment.

# Methods

### Participants and Setting

This study was conducted between July and December 2018, involved qualitative interviews with a purposeful sample of practicing pediatric nephrologists, managing pediatric and adult patients diagnosed with dRTA, and caregivers of the pediatric patients residing in the United States.

The four board-certified nephrologist had extensive experience in managing dRTA. Patients were required to have a confirmed diagnosis of dRTA and had to be ≥ 6 months of age and ≤ 65 years of age at the time of the interview for the patient or caregiver to be eligible to participate.

Patients and caregivers provided written informed consent prior to being interviewed. Institutional Review Board (IRB) approval was obtained from Quorum Review IRB. All study materials were reviewed and approved prior to patient recruitment. Patients and caregivers were recruited through interviewed nephrologists and social media groups.

### Data Collection

Interviews were conducted via telephone or WebEx by study staff trained in interviewing, study-specific aims, and interview administration procedures. Nephrologists and adult patients were each interviewed for approximately 60 minutes. Each pediatric patient was interviewed for approximately 10 minutes at the beginning of the interview, and the remainder of the interview, approximately 50 minutes, was conducted with the caregiver. Semi-structured interview guides were used to facilitate discussion during the interviews (see *supplementary material*). Topics covered during the nephrologist interviews included an overview of nephrologists' patient population, symptoms and impacts of dRTA, diagnosis, and management of dRTA with current SoC. Patient and caregiver interviews included a discussion of symptoms and impacts, diagnosis, and treatment with current SoC. Basic demographic information from the participants was collected during the interviews.

### Data Analysis

Interview audio-recordings were transcribed verbatim for analysis with Atlas.ti[10], a qualitative analysis software program used to help organize and code the data. Transcripts were qualitatively analyzed using a thematic approach to identify concepts and themes.[11] A structured codebook based on the interview guide was used to code the transcripts, with additional codes added as needed during the analysis. Demographic information was summarized using descriptive statistics.

## Results

### Participant Demographics

Four nephrologists, averaging 15 years' experience treating pediatric and adult patients with dRTA in an established hospital setting practice were interviewed. Table 1 provides a summary of the nephrologist sample.

Table 1
Nephrologist Demographics (N = 4)

| | |
|---|---|
| **Gender** | |
| Male | 2 (50%) |
| Female | 2 (50%) |
| **Specialty** | |
| Pediatric Nephrology | 4 (100%) |
| **Years of experience** | |
| Less than 10 years | 1 (25%) |
| 10–20 years | 2 (50%) |
| Over 20 years | 1 (25%) |
| **Setting** | |
| Hospital | 4 (100%) |
| *Note: One of the pediatric nephrologists saw both pediatric and adult patients* | |

Two adult patients (≥ 18 yrs. of age), a pediatric patient (7–14 yrs. of age) and caregiver pair, and one caregiver of a pediatric patient were interviewed. The patient population had an equal gender and race distribution (Caucasian: Hispanic/Latino). There was also an equal gender distribution among interviewed caregivers, both of whom were middle-aged, of Hispanic/Latino origin, employed full-time, and held a post-graduate degree. Patient and caregiver demographics are summarized in Table 2.

Table 2
Patient and Caregiver Demographics

| **Patient Demographics (N = 4)** | |
|---|---|
| **Gender** | |
| Male | 2 (50%) |
| Female | 2 (50%) |
| **Race** | |
| White, Caucasian | 2 (50%) |
| Hispanic or Latino | 2 (50%) |
| **Age** | |
| 0–6 years | - |
| 7–14 years | 2 (50%) |
| 15–17 years | - |
| 18 years or above | 2 (50%) |
| **Highest Level of Education** | |
| Elementary school | 2 (50%) |
| Associate's degree | 1 (25%) |
| Bachelor's degree | 1 (25%) |
| **Employment** | |
| Full-time | 1 (25%) |
| Disability | 1 (25%) |
| N/A (e.g., not of working age) | 2 (50%) |
| Caregiver Demographics (N = 2) | |
| **Gender** | |
| Male | 1 (50%) |
| Female | 1 (50%) |
| **Race** | |
| Hispanic or Latino | 2 (100%) |

*Note: In the case of one pediatric patient only the caregiver was interviewed, but demographic information was collected for both.*

| Patient Demographics (N = 4) | |
|---|---|
| **Age** | |
| 30–40 years | 1 (50%) |
| 50–60 years | 1 (50%) |
| **Highest Level of Education** | |
| Post-graduate degree | 2 (100%) |
| **Employment** | |
| Full-time | 2 (100%) |
| *Note: In the case of one pediatric patient only the caregiver was interviewed, but demographic information was collected for both.* | |

## Thematic Analysis

Three primary themes emerged from the analysis of the interviews: (1) diagnostic challenges, (2) burden of disease, and (3) burden of treatment with current SoC, as presented hereafter, including subthemes emerging from the quotations illustrated in Box 1 and Fig. 1.

### Diagnostic Challenges

Rare disorders pose a diagnostic challenge for physicians, which translates into a diagnostic odyssey for many patients. Pediatric nephrologists typically make the diagnosis of distal RTA in children 2–3 years of age. However, misdiagnosis or under-diagnosis was recognized as a common challenge by nephrologists, as some patients present with mild manifestations due to being partially compensated for the acidosis or have incomplete forms of dRTA and/or forms that are secondary to other conditions.

Nephrologists also commented regarding the heterogeneity in signs and symptoms by age. Gastric reflux, vomiting, and failure to thrive/poor growth are more common clinical manifestations among pediatric patients, whereas kidney stones, short stature, rickets, muscle cramping, and nephrocalcinosis are more common among adolescents and adults.

Patients and caregivers added to the narrative regarding the diagnostic journey by highlighting their personal struggles with dRTA, such as misdiagnosis, uncertainty in diagnosis, and late diagnosis occurring in adulthood.

See Box 1 for illustrative quotes regarding the diagnosis process.

### Burden of Disease

The overall burden of disease in patients with dRTA stems largely from metabolic acidosis and the resultant hypokalemia. Clinically this is characterized by poor growth or failure to thrive, kidney stones

and associated pain, nephrocalcinosis and decreased renal function, and hearing impairment in certain hereditary forms. Additional signs and symptoms include gastric reflux, nausea or vomiting, gastroenteritis, bowel dysfunction, decreased GI motility, hematuria, high urine output, urinary obstruction, muscle weakness and/or cramping, and fatigue.

Negative impacts were reported on domains including physical health and functioning, social and emotional functioning, health-related quality of life (HRQoL) and parenting challenges. Illustrative quotes regarding the disease burden are shown in Box 1.

### Physical Health

As a result of the metabolic imbalance seen in patients with dRTA, dietary restrictions, which include a low-sodium diet and avoiding high oxalate foods, are mandated to prevent the formation of kidney stones.

Nephrologists discussed the consequences of acidosis resulting in poor appetite or poor feeding in toddlers or infants, which could decrease growth beyond the negative impact on growth velocity caused by dRTA. Patients and caregivers also lamented the negative impact of weight fluctuations, and a weakened immune system leading to frequent infections.

### Physical Functioning Impacts

Adult patients reported limitations in their activities of daily living (ADLs) and physical activities due to fatigue caused by dRTA. Caregivers also reported that their child experienced limitations in their ADLs and physical activities (e.g., requiring a leg brace during sports) due to dRTA. Nephrologists noted the potential physical functioning limitations and impacts associated with dRTA, such as difficulty walking due to rickets and physical activity limitations due to short stature (e.g., not being able to participate in certain sports and activities).

### Social Functioning Impacts

Adult patients mentioned negative impacts on social functioning, such as changes in friendships, while caregivers mentioned the need for special care at school and disruptions to family activities. Nephrologists have observed the social impacts experienced by patients with dRTA that included difficulty with social interactions, isolation from peers, poor romantic relationships due to self-esteem issues, and lack of discipline resulting from being medicalized by their caregivers.

### Emotional Functioning Impacts

Negative impacts to emotional health reported by patients and caregivers include emotional breakdowns, increased stress from coping with a chronic rare disorder, and concerns about disease progression. These identified emotional functioning impacts were a reported cause of worry and frustration.

The emotional impact of dRTA extends beyond the patients themselves (e.g., an adult patient recounted the concern and worry that dRTA placed on his spouse). In addition, caregivers mentioned multiple

emotional impacts of dRTA on their own mental status, including emotional breakdowns and worry about their child (e.g., kidney stones, child having to take medications forever, etc.).

### Health-Related Quality of Life Impacts

The burden of disease extends beyond the patients' abilities to function, impacting their overall HRQoL.

The most burdensome HRQoL impacts cited by patients and caregivers with dRTA are the increased time and energy spent on doctor visits, hospitalizations, and surgeries. These are seen as limiting and disruptive to their lives thus, having a negative impact on their HRQoL. Such experiences are consistent with other rare diseases. Nephrologist comments mirrored patient and caregiver descriptions, adding that the need for hearing aids and poor growth/short stature also impacted patients' HRQoL.

### Parenting Challenges

Parenting challenges, such as special treatment or differential care given to the child with dRTA compared to their siblings were highlighted by caregivers. It was also suggested that parents of patients with dRTA sometimes experience increased marital discord and divorce rates or an alteration in family dynamics due to caregiver's diminished ability to discipline the child with RTA.

Adult patients also experienced challenges as parents and future parents, in particular the impact of dRTA on family planning due to the disease itself or the concern of having another child with dRTA.

### Professional and Educational Challenges

Patients and caregivers also reported limitations on adult patients' professional life or pediatric patients' academic life (e.g., limiting involvement in career-related activities or missing school) due to dRTA. Patients living with dRTA also expressed a substantial financial burden due to the cost of their SoC medications.

Nephrologists provided an additional perspective, emphasizing the long-term consequences (i.e., impact on child's cognitive development) associated with the discontinuity in schooling as a result of living with dRTA. Nephrologists mentioned that failure of dRTA patients to wear required hearing aids could also have a profound impact on their education.

### Burden of Treatment

Current dRTA medication SoC imposes a significant treatment burden leading to adherence challenges. Nephrologists, patients and caregivers expressed similar views on therapeutic unmet patient needs.

### Burden of Current SoC

Nephrologists acknowledged the burden of treatment and stressed the importance of good adherence to treatment for the successful management of dRTA. Patients failing to adhere to prescribed dosing regimens (time adherence and dose adherence) and patients who chronically miss doses, which occurs more frequently at night, can result in complications due to metabolic acidosis and hypokalemia.

Among the reasons for poor adherence that nephrologists commented included the challenges associated with i) the need for multiple medications and ii) maintaining medication schedules to manage the electrolyte disturbances.

Also, as patients grow and increase in weight, they have to increase their pill and/or liquid medication intake over time, making it difficult to keep track of both the number of medications and the frequency of dosing.

Poor palatability and tolerability of current SoC medication (e.g., unpleasant taste and GI upset or gastric reflux) were additional reasons for poor medication adherence. These issues are relevant to patients of any age, including infants who are unable to verbalize or express dislike for medication and may regurgitate medication.

In addition, adolescents are more likely to be non-adherent due to the fact that they either do not want to take a medication that makes them appear to be different from their peers or simply do not like the idea of taking medication.

See Box 1 for illustrative quotes regarding burden of treatment.

### Unmet Treatment Needs

Nephrologists noted dosing frequency, efficacy duration, side effects, and palatability as important limitations of current SoC. Of those limitations, decreasing the dosing frequency during the night was considered the most important unmet need.

As a result, nephrologists noted that formulations of alkali therapy addressing tolerability and palatability issues, with a longer duration of action, would have a positive impact on managing dRTA, offering the potential to improve metabolic control.

Patients and caregivers described the same unmet needs as the nephrologists, including less frequent dosing to avoid night-time awakenings and a formulation with reduced side effects. They also mentioned their dislike for current SoC medications (e.g., taste and dosing intervals), indicating an unmet need for a more palatable alkali therapy.

Figure 1 displays illustrative quotes highlighting important unmet needs of the current dRTA SoC.

# Discussion

Interviewed participants provided valuable insights into the dRTA lived experience. Nephrologists provided a broader overview of patient experience and more precise insights on the clinical manifestations, diagnostic challenges, and treatment of the disease, while patients and caregivers provided more insights into specific emotional and physical issues and day-to-day challenges.

The first challenge for patients and caregivers is often getting an accurate diagnosis and expert assistance navigating the healthcare system. This study highlights these challenges by providing an understanding of the dRTA diagnostic odyssey. Some difficulties in confirming a diagnosis may be associated with the different etiologies of dRTA and heterogeneity of symptoms. Early in life, some patients with dRTA who have variants in subunits of the vacuolar ATPase may present with features of proximal tubular dysfunction, which may lead to an erroneous diagnosis of renal Fanconi syndrome.[4]

In acquired forms, dRTA is caused by autoimmune diseases (e.g., Sjögren syndrome or systemic lupus erythematosus) or secondary to other conditions. [12,13,14] Symptoms may present with a late onset amidst many other symptoms related to the main condition, which complicates diagnosis.

Another challenge may be associated with the presence of incomplete features of dRTA, such as in heterozygous carriers of hypofunctional vacuolar ATPase, and can present with recurrent kidney stones and nephrocalcinosis in adulthood.[15]

Additionally, there are forms of dRTA with deafness or late-onset deafness.[16] Regular hearing examination in all patients should be performed, since sensorineural hearing loss can occur later in life and is not always predicted by genetic signature.[4]

Improved disease awareness and diagnostic algorithms including confirmatory diagnostic evaluations and/or genetic tests are required. In a recent survey conducted in Spain with 40 nephrologists, only 13.3% of the responders performed confirmatory genetic testing and 11.1% performed pedigree studies when suspecting dRTA. [17]

The significant burden of disease is illustrated by the negative impacts related to patients' physical health and functioning (e.g., appetite changes and weight gain/loss, frequent infections, fatigue, limitations in physical activities), social and emotional functioning (e.g., anxiety/worry, coping mechanisms, occurrences of marital discord), HRQoL (e.g., chronic treatments, frequent blood tests, difficulty traveling, need for hearing aids), and academic or professional life (e.g., limiting involvement in career-related activities or missing school). These important impacts are generally not covered in the scientific literature and highlight areas where management of dRTA can be improved.

Lastly, this study demonstrates that current SoC has limitations, recognized by patients, caregivers, and nephrologists, which may lead to suboptimal dosing and poor medication adherence. Adherence is a key factor for any treatment success[18] and in the case of dRTA, decreased therapeutic adherence, leading to poor metabolic control, could hasten disease progression.[17]

For most chronic diseases reported in developed countries, approximately 50% of patients adhere to treatment recommendations.[19] However, among patients with dRTA, the aforementioned published survey reports only 27% of the nephrologists reported excellent or very good adherence among this population. [17] These findings underscore that there remain significant adherence challenges presented by

current standard of care. Our interview findings suggest that tolerability issues, bad taste, and the required frequency of dosing with existing medications for dRTA could be at the origin of most adherence issues in these patients. These findings help support the need for therapeutic alternatives with a longer dosing interval[20], improved safety, and gastrointestinal tolerability and palatability, for treatment of dRTA.[21, 22]

It has been reported that adherence to treatment declines as the number of daily doses increases, particularly in the case of chronic diseases.[23, 24, 25] Multiple medications may also be problematic, and fixed combinations simplifying treatment have been reported to improve adherence.[26]

Thus, improvements in the number of doses and frequency of dosing compared to current SoC are likely to result in improved adherence to therapy and better overall health outcomes.[18, 27]

The small sample size of patients and caregivers is a limitation of this study, in part due to the low prevalence of this rare disease[1, 2] and the lack of central patient advocacy groups. No adolescent patients or their caregivers were interviewed, and our sample was limited geographically to the United States. Furthermore, as a cross-sectional study, interviews were conducted at a single point in time, and the results may have been subject to recall bias when participants were asked about past events. Longitudinal qualitative interviews at multiple time points could overcome this bias and expand understanding of changes in patient and caregiver experiences over time.[28, 29] However, the sample includes patients, caregivers and nephrologists, representing many stakeholders in dRTA.

A major strength of this study is that it captures insights from the nephrologist, patient, and caregiver perspectives. Together, these testimonies provide a more holistic understanding of the dRTA disease burden.

In conclusion, these findings aim to bridge the gap in knowledge regarding the dRTA patient lived experience and caregiver experience and provide suggestions for improvements to clinical practice by emphasizing the need for increased recognition of dRTA through improved diagnostic algorithms. These findings highlight the significant challenges affecting the patient and caregiver on a daily basis and accentuate the need for a more tolerable, longer-acting alkali therapy offering round-the-clock coverage providing improved clinical outcomes.

# Declarations

*Article information*

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*Authors' contributions*

AM, LL and PK were responsible for the conception and design of the study and provided support and guidance throughout the project. SS conducted the interviews and led on the analysis of the data. SS, PK, AM developed the coding framework. SS coded all transcripts and summarized interpretation of the study data with help of PK, and AM. AM, LL, PK and SS discussed the analysis and interpretation of the data. Each author contributed to drafting the manuscript or revising it critically for important intellectual content. Authors accept accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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*Availability of data and materials*

Data supporting the conclusions in this article are included within the article itself. Further data is available from the corresponding author on request.

*Ethics approval*

The research was approved by Quorum Review IRB (project ID 4331/0002). All study materials were reviewed and approved prior to patient recruitment.

*Consent for publication*

Patients and caregivers provided written informed consent (including consent for the use of anonymized quotes in Publications) prior to being interviewed Informed consent was obtained by all participants prior to interview.

*Competing interests*

M.A. Manso-Silván is an employee of Advicenne and holds stock options/shares in the company. C. Ogg is an employee to Advicenne. L. Law was a consultant to Advicenne at the time of the study. C D'Alessandri- Silva was on the SAB for Advicenne at the time of the study. AM, PK and SS, employees of Mapi at the time the study was conducted, are paid consultants of Advicenne. The remaining authors declare that they have no relevant competing interests.

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# Figures


**Figure 1**

Figure 1 is not included with this version of the manuscript.