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Distal renal tubular acidosis: ERKNet/ESPN clinical practice points

Francesco Trepiccione[1,*], Steven B. Walsh[2,*], Gema Ariceta[3], Olivia Boyer[4], Francesco Emma[5], Roberta Camilla[6], Pietro Manuel Ferraro[7,8], Dieter Haffner[9], Martin Konrad[10], Elena Levtchenko[11], Sergio Camilo Lopez-Garcia[2,12], Fernando Santos[13], Stella Stabouli[14], Maria Szczepanska[15], Velibor Tasic[16], Rezan Topaloglu[17], Rosa Vargas-Poussou[18], Tanja Wlodkowski[19] and Detlef Bockenhauer[2,12]

[1]Department of Translational Medical Sciences, University of Campania 'L. Vanvitelli', Naples, Italy, [2]Department of Renal Medicine, University College London, London, UK, [3]Division of Pediatric Nephrology, Hospital Universitario Vall d'Hebron, Universitat Autonoma de Barcelona, Barcelona, Spain, [4]Pediatric Nephrology, Necker Hospital, APHP, MARHEA, Imagine Institute, Paris University, Paris, France, [5]Division of Nephrology, Bambino Gesu Children's Hospital—IRCCS, Rome, Italy, [6]Nephrology, Dialysis, Transplantation, Regina Margherita University Hospital, Turin, Italy, [7]U.O.S. Terapia Conservativa della Malattia Renale Cronica, U.O.C. Nefrologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, [8]Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy, [9]Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School Children's Hospital, Hannover, Germany, [10]Department of General Pediatrics, University Children's Hospital, Muenster, Germany, [11]Division of Pediatric Nephrology, University Hospitals Leuven and Department of Development and Regeneration, Katholieke Universiteit Leuven, Leuven, Belgium, [12]Renal Unit, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK, [13]Department of Pediatrics, Hospital Universitario Central de Asturias and Área de Pediatría, Dpto de Medicina, Universidad de Oviedo, Oviedo, Spain, [14]First Department of Pediatrics, Aristotle University, Thessaloniki, Greece, [15]Department of Pediatrics, SMDZ in Zabrze, SUM in Katowice, Zabre and Katowice, Poland, [16]University Children's Hospital, Medical School, Skopje, Macedonia, [17]Department of Pediatric Nephrology, Hacettepe University Faculty of Medicine, Hacettepe University, Ankara, Turkey, [18]Department of Genetics, Centre de Références MARHEA, Hôpital Européen Georges Pompidou Assistance Publique Hôpitaux de Paris, Paris, France and [19]Department of Paediatric Nephrology, University Children's Hospital, Heidelberg, Germany

*These authors contributed equally to this work.
Correspondence to: Detlef Bockenhauer; E-mail: d.bockenhauer@ucl.ac.uk

ABSTRACT

Distal renal tubular acidosis (dRTA) is characterized by an impaired ability of the distal tubule to excrete acid, leading to metabolic acidosis. Associated complications include bone disease, growth failure, urolithiasis and hypokalaemia. Due to its rarity, there is limited evidence to guide diagnosis and management; however, available data strongly suggest that metabolic control of the acidosis by alkali supplementation can halt or revert almost all complications. Despite this, cohort studies show that adequate metabolic control is present in only about half of patients, highlighting problems with treatment provision or adherence. With these clinical practice points the authors, part of the working groups tubulopathies in the European Rare Kidney Disease Reference network and inherited kidney diseases of the European Society for Paediatric Nephrology, aim to provide guidance for the management of patients with dRTA to facilitate adequate treatment and establish an initial best practice standard against which treatment of patients can be audited.

Keywords: acidosis, distal renal tubular acidosis, nephrocalcinosis, urolithiasis

INTRODUCTION

Distal renal tubular acidosis (dRTA) is characterized by an impaired ability of the distal tubule to excrete acid and can be primary, due to pathogenic variants in genes involved in acid excretion, or secondary, associated with acquired damage to the distal tubule [1]. Typical complications of dRTA include bone manifestations, such as rickets or osteomalacia due to buffering of acid by hydroxyapatite in the bone [2]. The excess calcium dissolved from the bone is excreted in the urine resulting in nephrocalcinosis and/or urolithiasis [3]. In children, growth failure is a common presentation [4]. Hypokalaemia is another typical manifestation and can be associated with muscle weakness or even paralysis [5]. Chronic kidney disease (CKD), especially stages 2 and 3, are more prevalent and occur at an earlier age than in the general population [6].

Treatment is typically provided by alkali supplementation to buffer the excess acid. Importantly, adequate treatment resolves (rickets, osteomalacia, growth failure and muscle weakness) or at least slows or arrests (CKD and nephrocalcinosis) disease manifestations [4, 7, 8]. Thus, dRTA is a treatable disease! Yet, in one large cross-sectional study, only about half of all patients had evidence of adequate treatment [7], highlighting the need for better awareness and treatment of dRTA to meet the needs of patients affected by this rare disorder. As part of the working groups tubulopathies in the European Rare Kidney Disease Reference network (ERKNet) and inherited kidney diseases of the European Society for Paediatric Nephrology (ESPN), we set out to review current evidence and provide expert recommendations.

Pathophysiology and classification

In healthy kidneys, urinary acidification occurs via active secretion of H^+ by the H^+-ATPase, expressed on the apical membrane of the intercalated cells in the collecting duct [9]. Bicarbonate generated in this process is returned to the circulation via the basolateral anion exchanger AE1 (Figure 1).

Clinically, two different forms of dRTA can be distinguished: the 'classical' or 'type 1' RTA, which reflects a primary impaired distal tubular acid secretion, and the 'hyperkalaemic' or 'type 4' RTA, which is a secondary complication of an impaired ability to reabsorb Na^+ in the collecting duct, such as seen with (pseudo)hypoaldosteronism [10, 11]. In this expert opinion, we will only address the 'classical' or 'type 1' RTA. The characteristic biochemical phenotype of this primary impaired acid secretion is a hypokalaemic, hperchloraemic metabolic acidosis with inappropriately alkaline urine (see the 'Diagnosis' section).

There are primary (Mendelian) and secondary (acquired) forms of dRTA. Primary dRTA is estimated in one study to have a prevalence of <1:100 000 [12].

Secondary dRTA is most commonly associated with autoimmune diseases, especially Sjögren's syndrome (SS). While also rare, the prevalence in one study has been estimated at roughly 10 times that of primary dRTA [13].

MATERIALS AND METHODS

Development of these Clinical Practice Points is an initative of ERKNet and the ESPN, spanning from 2019 until 2021, and involved two meetings, which were held online due to the ongoing COVID-19 pandemic. Two groups were assembled: a core leadership group and a voting panel. The core leadership group included paediatric and adult nephrologists and geneticists. Working groups focusing on specific topics were formed. A systematic literature search was performed (for details, see Supplementary data, Table S2). Statements were elaborated and discussed by experts according to their level of agreement after literature review. Due to the rarity of the disease and the poor level of evidence, these statements could not be graded. The voting group included seven members of the ESPN and ERKNet with expertise in paediatric and adult dRTA or genetic testing. Voting group members were asked by use of an e-questionnaire to provide a level of agreement on a 3-point scale (agree, disagree and unsure) (Delphi method). A minimum 70% level of consensus was required for final adoption of recommendations.

Clinical characteristics and diagnostic assessment

Diagnosis. In a patient with symptoms suggestive of dRTA (Table 1), we recommend to obtain comprehensive clinical, biochemical and radiological information (Table 2) to ascertain the underlying diagnosis.

An overview of age-specific potential symptoms is given in Table 1. The characteristic biochemical features of dRTA are the combination of normal anion gap hyperchloraemic metabolic acidosis with an inappropriately elevated urine pH (>5.5) with a positive urine anion gap (see Appendix 1.1) in the absence of advanced CKD (CKD stage <4). Hypokalaemia and hypercalciuria are further typical findings and radiographic assessment usually shows nephrocalcinosis and/or nephrolithiasis [14]. In addition to the listed biochemical data, some clinicians assess additional markers, such as urinary citrate and pCO_2 (see Supplementary data, Appendices 1.4 and 1.5). An algorithm for

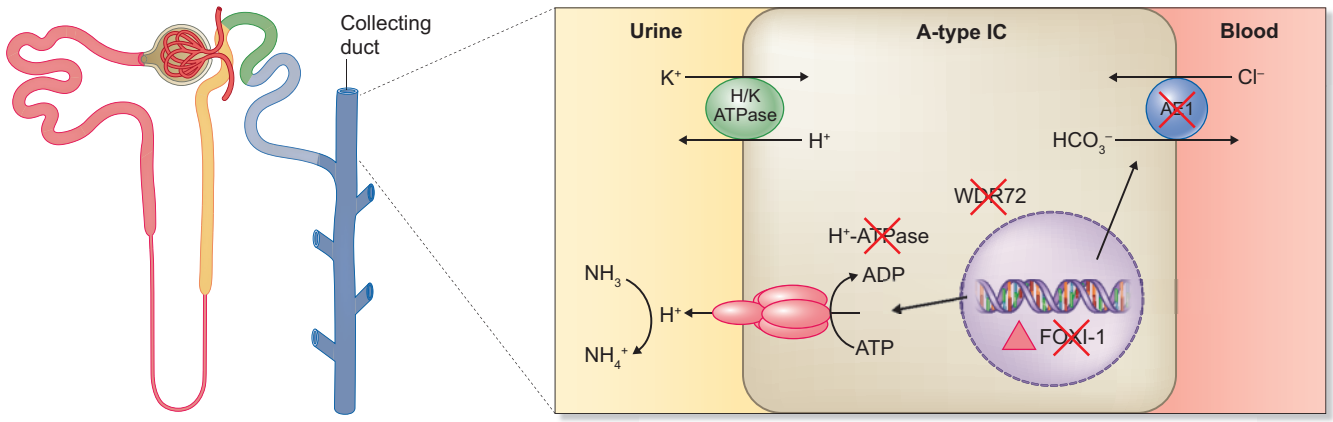

FIGURE 1: Molecular basis of dRTA. Shown is a type A intercalated cell (IC) in the collecting duct. Intracellular carbonic acid dissociates into H^+ (secreted into the tubular lumen by the H^+-ATPase) and HCO_3^- (reabsorbed into the blood by the anion exchanger AE1/SLC4A1). Marked with red crosses are proteins associated with dRTA. Two subunits of the heteromultimeric H^+-ATPase, ATP6V1B1 and ATP6V0A4 are associated with autosomal recessive dRTA. Their expression is regulated by the transcription factor FOXI1. The mechanisms by which variants in WDR72 cause dRTA have yet to be clarified.

Table 1. Age-specific symptoms in patients with dRTA

Age category	Potential presenting symptoms
Infants	Failure to thrive and growth retardation
	Polyuria/polydipsia[a]
	Vomiting
	Constipation
	Dehydration (sometimes with fever episodes)
	Rickets
	Hypotonia
	Nephrocalcinosis
	Haemolytic anaemia (spherocytosis/ovalocytosis)[b]
	Sensorineural hearing loss[c]
Children and adolescents	Growth retardation
	Polyuria/polydipsia[a]
	Rickets
	Vomiting
	Constipation
	Dehydration
	Muscle weakness/hypokalaemic paralysis
	Haemolytic anaemia (spherocytosis/ovalocytosis)[b]
	Sensorineural hearing loss[c]
	Nephrocalcinosis and/or urolithiasis
	Enamel defects[4]
Adults	Nephrocalcinosis and/or urolithiasis
	Osteomalacia (may be misreported as osteoporosis)
	Muscle weakness, hypokalaemic paralysis
	Bone pain
	Fractures
	Haemolytic anaemia (spherocytosis/ovalocytosis)[b]
	Sensorineural hearing loss[c]
	Nephrocalcinosis and/or urolithiasis
	Enamel defects[d]
	In patients with secondary dRTA symptoms of the primary immune disorder: SS, systemic lupus erythematosus, Graves' disease

Presenting symptoms of dRTA are highly variable and non-specific and there should be a low index of suspicion for initial blood tests. Almost all patients have metabolic acidosis and hypokalaemia at initial presentation, except for some, mostly adult patients with secondary dRTA, who may present with normal blood pH and bicarbonate, but an impaired ability to acidify the urine (idRTA).

[a]Up to two-thirds of infants and children present with additional proximal tubular dysfunction, which resolves with treatment [4].

[b]Haemolytic anaemia is seen in patients with specific *SLC4A1* variants (see Supplementary data, Appendix 5.2: Red cell disorders).

[c]Early-onset sensorineural deafness is typically associated with pathogenic variants in *ATP6V1B1* and *FOXI1*. Hearing loss in patients with ATP6V0A4-associated disease is variable and can manifest as early as in infancy or not at all (see Supplementary data, Appendix 5.1: Sensorineural deafness).

[d]Enamel defects (AI) is only associated with pathogenic variants in WDR72.

Table 2. Clinical and biochemical parameters for diagnosis and follow-up: listed are recommended parameters for assessment at diagnosis and follow-up of patients with dRTA

	Initial evaluation	Follow-up[a]
Clinical		
All patients: Absence of extrarenal bicarbonate loss (e.g. diarrhoea, stoma and laxative abuse)	√	
Children: presence of growth failure	√	√
Adults: history of autoimmune disease, especially SS	√	√
Children: height and weight, evidence of rickets	√	√
Adults: frequency of stone episodes		√
Biochemistries		
Blood: Na^+, K^+, Cl^-, HCO_3^-[b], urea, creatinine, calcium, magnesium, phosphate, pH	√	√
Spot urine: Na^+, K^+, Cl^-, pH, creatinine, calcium	√	√
Calculations		
$U_{Ca/Crea}$ ratio[c], eGFR	√	√
Urine anion gap	√	
Imaging		
Renal ultrasound: nephrocalcinosis/ lithiasis?	√	√
Wrist and/or knee/or ancle radiographs (rickets)[d]	√	
Molecular genetics		
Analysis of causative genes[e]	√	

The diagnosis of dRTA is based on an association of clinical, biochemical and radiographic findings and confirmed by genetic analysis. For calculation and assessment of urine anion gap, see main text.

[a]Frequency of follow-up depends on the stability of the patient: for stable patients with no change in dosage and no apparent stone disease, 6-monthly (paediatrics) or annual (adults) follow-up may be sufficient. In newly diagnosed patients and those with rapid growth (paediatrics) or unstable biochemistries, more frequent follow-up (every 1–3 months) is recommended.

[b]HCO_3^- can be measured directly (as total CO_2) or assessed indirectly via a venous blood gas analysis.

[c]There are no data to suggest superiority of a spot urine calcium/creatinine ratio versus a 24-h urine calcium collection. See also Supplementary data, Appendix 6.1.

[d]In children in case of clinical signs of rickets or markedly elevated ALP.

[e]In case that the above clinical and biochemical parameters support the diagnosis of dRTA.

the assessment and diagnosis of patients with metabolic acidosis is presented in Figure 2. The differential diagnosis is discussed in detail in the Supplementary data, Appendix 2.

Hyperchloraemic non-anion gap acidosis. The biochemical picture of dRTA is characterized by a non-anion gap metabolic acidosis, the severity of which is highly variable between patients. Reported blood pH at presentation varies between 6.7 and 7.4 and bicarbonate levels between 5 and 20 mmol/L with correspondingly elevated chloride levels, so that the anion gap remains normal [4, 15]. Acidosis is typically more pronounced in patients with recessive forms of dRTA [6] (for further details, see Supplementary data, Appendix 1.1).

Hypokalaemia. Hypokalaemia is a characteristic feature in dRTA and, in untreated patients, is often pronounced (<3.0 mmol/L). In some patients, especially with SS, hypokalaemia complicated by severe muscular weakness and paralysis may be the presenting feature of dRTA. The pathophysiology of hypokalaemia in dRTA is thought to be due to two key mechanisms [16]:

- Systemic acidosis *per se* leads to renal K^+ wasting, as acidosis decreases sodium reabsorption in the proximal tubule with consequent volume contraction and activation of the renin–angiotensin–aldosterone system [17].
- An increased voltage gradient in the collecting duct generated by the uptake of Na^+ via epithelial sodium channel and not balanced by the secretion of protons [18].

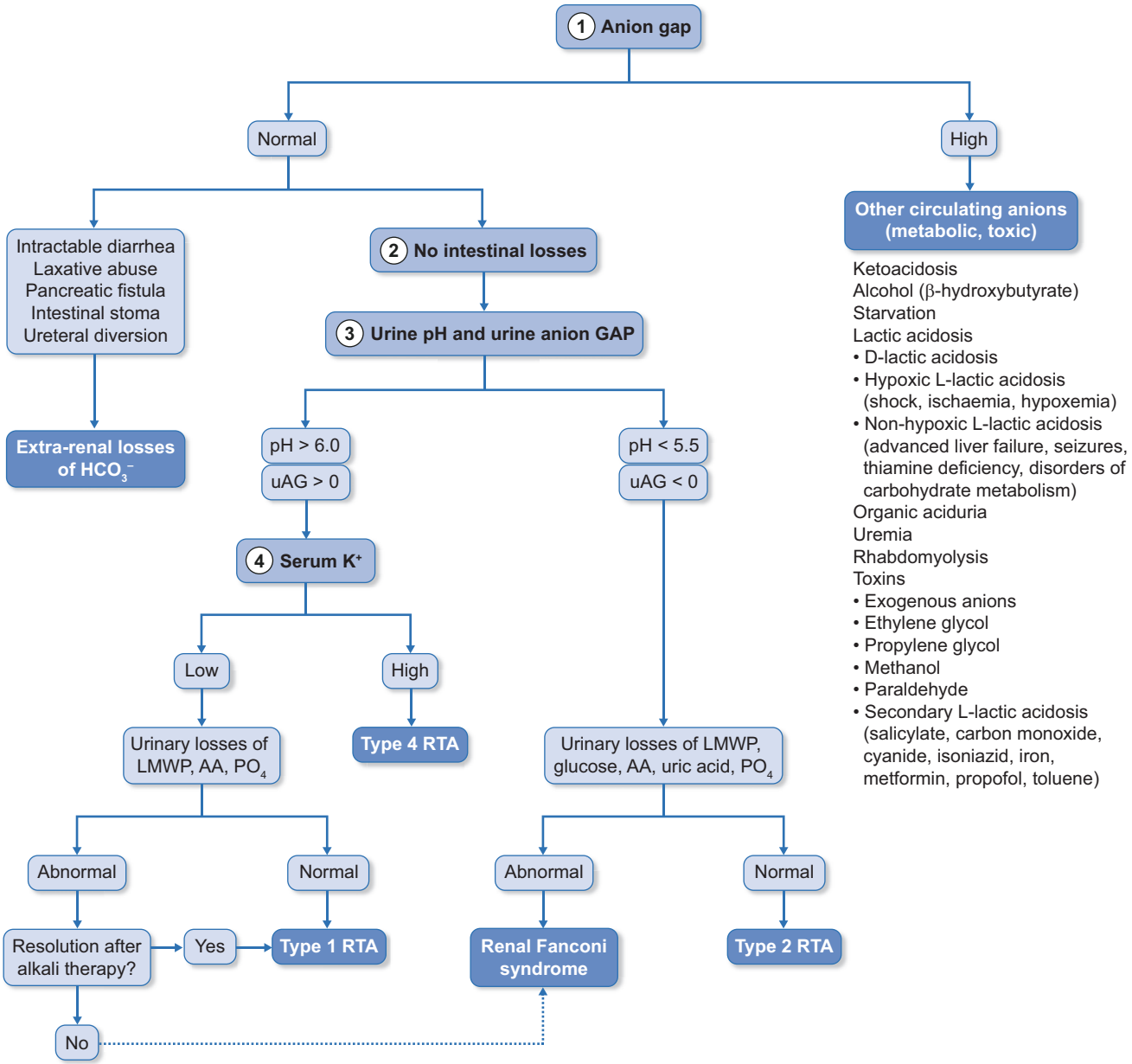

FIGURE 2: An algorithm for assessment and diagnosis of a patient with metabolic acidosis. Note the four critical decision steps: (1) presence of an anion gap to identify patient with acid gain, rather than bicarbonate loss; (2) distinction between gastrointestinal and renal bicarbonate loss; (3) urine pH and urine anion gap (uAG) to distinguish between proximal and distal RTA; and (4) plasma potassium, to distinguish between type 1 (classical) and type 4 (hyperkalaemic) dRTA. LMWP, low molecular weight protein; AA, amino acid.

In some acquired forms, such as with administration of amphotericin B, there may also be leakage of potassium into the tubular lumen.

Urine pH. Failure to acidify the urine with systemic acidosis is a key feature of dRTA [1]. Consequently, the measurement of urine pH is critical for the diagnosis. Initial publications identified a pH of <5.3 as consistent with maximal acidification [19]. However, in clinical practice, pH is often assessed by dipstix, so that a limit of 5.5 is used (see Supplementary data, Appendix 1.3). In primary dRTA, urine pH is usually well above this value.

Acidification of the urine has two key components:

- Reabsorption of filtered HCO_3^-, 80–90% of which occurs in the proximal tubule, the remaining part is reclaimed mostly in the thick ascending limb of Henle's loop [1]. Complete reabsorption of filtered HCO_3^- results in a decrease of urine pH to approximately 6.
- Secretion of protons in the distal nephron, primarily the collecting duct. In the healthy individual, this distal acidification can lower the urine pH to a range of 4.5–5.5. Thus, failure to acidify the urine below 5.5 despite systemic acidosis highlights a problem with distal acidification.

Urine anion gap. The urine anion gap (uAG = $Na^+ + K^+ - Cl^-$, measured in urine) indirectly reflects urinary ammonium excretion (see Supplementary data, Appendix 1.4). As H^+ in the urine is primarily buffered by NH_3 (ammonia) to form NH_4^+ (ammonium), the uAG can help to assess distal H^+ secretion. With normal acidification, the uAG is <0 with systemic acidosis [14]. There are multiple confounders in the interpretation of the uAG and there is no evidence that it adds information beyond that provided by urine pH [20].

Urinary concentration defect. Patients with medullary nephrocalcinosis of any cause tend to have a urinary concentration defect [21]. Very few studies have directly tested the urine concentration ability of patients with dRTA. In one study, 12 patients with a clinical diagnosis of distal RTA were found to have a significant impairment with a median value for maximum urine osmolality of 340 mOsm/kg [21]. The severity of this impaired concentrating ability, however, varied considerably. Nonetheless, physicians should be aware that patients with dRTA are potentially at higher risk of dehydration, particularly during episodes of vomiting or diarrhoea.

Hypercalciuria. The increased urinary excretion of calcium in dRTA is primarily a consequence of the systemic acidosis as excess protons are buffered by apatite in the bone, leading to release of calcium into the blood stream [2, 22]. In addition, animal experiments suggest that acidosis leads to tubular resistance to the anticalciuric effect of Parathyroid Hormone (PTH) [23] and reduced expression of Trpv5 [3, 24], resulting in a further net increase in fractional excretion of calcium.

Nephrocalcinosis/nephrolithiasis. The main inhibitor for calcium precipitation in the urine is citrate and acidosis enhances proximal tubular reabsorption of citrate, leading to hypocitraturia [25, 26]. The combination of hypercalciuria and hypocitraturia in dRTA strongly increases the risk of calcium precipitation. Indeed, nephrocalcinosis and/or urolithiasis are present in approximately 65% of patients [27] and this prevalence is even higher (90–100%) in patients with primary dRTA [4, 6, 7]. Nephrocalcinosis is typically present already at the initial presentation, but can be absent in those with dominant dRTA, if identified early in life due to family screening [4]. Nephrocalcinosis is absent on antenatal scans of affected pregnancies, consistent with clearance of excess acid by the placenta.

Similarly, nephrolithiasis is a common complication of dRTA, seen in approximately 20% of patients with primary dRTA and even 42% if associated with variants in *SLC4A1* [28]. The role of hypocitraturia in stone formation and the predominance of calcium–phosphate stones is discussed in the Supplementary data, Appendix 2.4.

Transient proximal tubular dysfunction. Untreated patients, typically infants with primary dRTA and severe acidosis at presentation, can have additional features of proximal tubular dysfunction, mainly low-molecular weight proteinuria, aminoaciduria and, less commonly, phosphaturia [4, 5, 29–31]. In one paediatric series, this selective proximal tubular dysfunction was noted in 67% of dRTA patients at presentation [4]. The aetiology is unclear, but is commonly ascribed to the hypokalaemic acidosis, as it resolves with potassium-alkali supplementation, typically within a few weeks and without additional treatment [5, 29]. Interestingly, glycosuria has so far not been reported in this transient proximal tubular dysfunction in dRTA and the presence of glucose in the urine would thus make a diagnosis of dRTA less likely [4].

Genetic testing. We recommend offering genetic testing to all patients with a clinical suspicion of primary dRTA.

The detection of (likely) pathogenic variants in one of the genes responsible is crucial to confirm the diagnosis of dRTA and for genetic counselling.

Benefits and analytical sensitivity of genetic testing are discussed in Supplementary data, Appendices 2.3 and 2.4.

Currently, five genes have been associated with dRTA, some of which also have extra-renal features (Table 3). Underlying genes were identified essentially in order of their prevalence: the most common causative gene, *SLC4A1*, encoding the anion exchanger AE1, was reported in 1997, followed by *ATP6V1B1* (1999) and *ATP6V0A4* (2000), both encoding subunits of the H^+-ATPase expressed on the apical membrane. Together, these three genes explain roughly 60–80% of primary dRTA [6, 7, 37, 38]. Causative variants in *FOXI1* have so far only been reported in two families [35]. Variants in *WDR72* as a cause of dRTA were first reported in 2018 in two families, but have been identified since in at least another four families [36, 38, 39]. *WDR72* had been previously associated with amelogenesis imperfecta (AI) [40]. The reported age of presentation in patients with *WDR72*-associated dRTA is between 4 and 12 years and the presenting symptom in some was AI, with dRTA only noted by 'reverse phenotyping', that is, further investigations prompted by the genetic result. Moreover, not all family members with *WDR72*-associated AI had clear evidence of dRTA [39]. This suggests that *WDR72*-associated dRTA is typically milder than in other recessive forms, which typically present in the first year of life with failure to thrive [7, 35]. In this regard, *WDR72*-associated dRTA is similar to the autosomal dominant form

Table 3. Genes associated with dRTA: listed are currently recognized genes associated with dRTA

Gene	Function	Phenotype MIM	Inheritance	Extra-renal features	Reference
SLC4A1	Anion exchanger (AE1)	179800	AD, AR	none	[32]
ATP6V1B1	V-type H^+ ATPase subunit B1	267300	AR	SND	[33]
ATP6V0A4	V-type H^+ ATPase subunit a4	602722	AR	±SND	[34]
FOXI1	Transcription factor FOXI1	N/A	AR	SND	[35]
WDR72	WD repeat-containing protein 72	N/A	AR	AI	[36]

MIM, Mendelian Inheritance in Man; AD, autosomal dominant; AR, autosomal recessive; SND, sensorineural deafness; AI, amelogenesis imperfect; N/A, not available.

(*SLC4A1*), which has a reported median age of presentation between 2 and 12 years and with younger patients often identified by family screening rather than obvious symptoms [7].

Genetic testing should be performed in a laboratory accredited for diagnostic genetic testing. Considering the genetic heterogeneity, the use of an next generation sequencing-based gene panel for parallel sequencing of all genes (in one test) is recommended, as well as the inclusion of relevant genes for the differential diagnosis of dRTA and/or nephrocalcinosis. Such panels may also be virtual, based on whole-exome/genome sequencing. Regularly updated panel suggestions are available online, such as https://panelapp.genomicsengland.co.uk/panels/149/.

If only a single variant has been identified in a recessive disease gene by sequencing, the analysis should be complemented with a test for a copy number variation. Yet, in 6–12% of patients, even after searching for large rearrangements, only one heterozygous pathogenic variant is discovered [4, 6, 7, 15, 37, 41, 42]. This includes heterozygous variants in *ATP6V1B1* causing the predicted missense change Arg394Gln, which have been recurrently identified in patients with dRTA and are typically *de novo* [7, 37]. It remains to be seen whether this variant is pathogenic on its own, or whether a second variant on the other allele has been missed by current diagnostic methods.

We recommend that a negative genetic test should prompt a careful review of clinical features to confirm the correct clinical diagnosis, as well as analysis of the relevant genes for the differential diagnosis.

It is important to note that with the increasing availability of new population-based genetic data and functional studies, the classification of variants may change: the pathogenicity of previously disease-associated genetic variants could be questioned and, vice versa, variants of previously uncertain significance could be confirmed as pathogenic [44].

Additional features that can help identify specific subtypes.

Hearing. For recessive dRTA linked to *ATP6V1B1*, *ATP6V0A4* or *FOXI1*, we recommend early and developmentally appropriate hearing screening. In addition, all patients at risk should have at least one diagnostic audiology assessment by 24–30 months of age. Patients with sensorineural hearing loss should have appropriate audiological follow-up.

Sensorineural deafness is seen in almost all patients with ATP6V1B1- and FOXI1-associated disease and approximately 40% of ATP6V0A4-associated dRTA (see Supplementary data, Appendix 5.1: Sensorineural deafness). Hearing impairment has not been reported in patients with recessive variants in *WDR72* [36, 38 39].

Data on the incidence of deafness related to *SLC4A1* are scarce. Two large studies reported hearing loss in ∼10% of patients with variants in *SLC4A1* [6, 7], roughly similar to the prevalence in the general population [45].

Since hearing loss in infants and children is linked to lifelong deficits in speech and language acquisition, poor academic performance, personal-social maladjustments and emotional difficulties, the early identification of hearing loss is important [46]. This is consistent with guidance from the American Academy of Pediatrics [47, 48].

Amelogenesis imperfecta. There is currently insufficient evidence to recommend that children with inherited dRTA related to genetic defects other than WDR72 should undergo a specific dental assessment for AI.

In 2018, recessive variants in WDR72 were identified in two families affected by dRTA and AI [36] and subsequently further families were reported [38, 39]. At this point it is not fully clear whether AI with dRTA is exclusively associated with WDR72, or whether further genes may be identified. However, this association has never been described in patients with dRTA due to variants in *ATP6V1B1*, *ATP6V0A4*, *SLC4A1* or *FOXI1*.

With regards to differential diagnosis, it is important to note that AI is associated also with other genes, including *CLDN16*, *CLDN19*, *SLC4A4* and *FAM20A*, that can phenocopy features of dRTA.

Haematologic anomalies. Some individuals with dRTA and specific variants in *SLC4A1* gene can have an associated haemolytic anaemia (see Supplementary data, Appendix 5.2: Red cell disorders).

Bone mineralization. We do not recommend routine assessment of bone mineralization by methods such as X-rays and dual energy X-ray absorptiometry (DEXA) in children with dRTA.

In adults, assessment of bone mineral density (BMD) by DEXA every 2–3 years may be helpful in assessing fracture risk and treatment adequacy.

There are no data available on bone mineralization in children with dRTA and only few in adults. In one study, 14 adult newly diagnosed Thai patients prior to commencement of alkali supplementation underwent systematic evaluation of bone histology and determination of BMD through DEXA: osteopenia or osteoporosis was present in all subjects, and average *T*-score values were considerably lower than in healthy controls; bone formation rates were lower and osteoid volume and surface higher, suggesting a condition of low bone turnover [49]. Importantly, a follow-up investigation of 10 of those patients showed that abnormalities in BMD and bone turnover parameters improved significantly after 1 year of alkali supplementation [50]. These data are consistent with the concept that bone abnormalities in dRTA arise as a consequence of the acidosis, due to buffering of excess protons by mobilization of calcium phosphate and calcium carbonate from the bone with consequent demineralization (see also the 'Hypercalciuria' section) and are reversible by alkali supplementation. In the absence of paediatric data and considering the difficulties of interpreting DEXA results in children, as bone density changes with age, we do not recommend routine BMD assessment in this age group. In contrast, many centres use DEXA imaging to assess BMD in adult dRTA patients, which informs fracture risk and treatment adequacy. In view of these potential benefits, it is reasonable to measure BMD in adults every 2–3 years.

Growth failure in dRTA and role of recombinant human growth hormone therapy. We do not recommend the use of growth hormone in children with dRTA, unless there is persistent growth retardation despite adequate metabolic control.

An association between dRTA and reduced growth has been reported in several paediatric studies [4, 6, 7, 51–57]. There is no evidence for a primary growth hormone deficiency in dRTA, but rather that metabolic acidosis in dRTA interferes with growth hormone secretion and leads to decreased serum insulin-like growth factor 1 [51, 53, 58]. Metabolic acidosis has no evident effect on IGF binding protein 3, but is associated with resistance to the hepatocellular action of growth hormone [59]. In addition, the presence of rickets has been associated with failure to reach normal adult height [55].

As these risk factors are modifiable with treatment, most patients achieve growth in the normal range and adequate control of the acidosis is associated with improved growth [4, 6, 7, 54, 55].

Incomplete dRTA. We recommend assessing urinary acidification in patients with nephrocalcinosis/lithiasis and low–normal/borderline low blood bicarbonate levels or hypocitraturia.

The term incomplete dRTA (idRTA) refers to an impaired ability to acidify the urine below 5.5 in the absence of overt metabolic acidosis. The defect in urine acidification in idRTA is typically less severe than in complete dRTA. idRTA has mostly been reported in adults and rarely in children [51, 52].

Typically, the suspicion of idRTA is raised by the presence of recurrent stones, nephrocalcinosis, osteoporosis or failure to thrive (children) in patients with borderline normal or intermittently low bicarbonate. Of note, the lower limit of the normal range for blood bicarbonate levels increases with age (see Supplementary data, Appendix 1.3).

idRTA was first described in a group of individuals with nephrocalcinosis, normal serum bicarbonate and inability to acidify urine beyond pH 5.3 during an oral ammonium chloride test [19]. Since the initial report multiple other authors have described a close relation between stone formation and idRTA [60, 61].

Due the absence of acidosis at baseline, idRTA cannot be demonstrated without provoking an acidosis (e.g. ammonium chloride test) or another stimulus to distal urinary acidification (e.g. the simultaneous furosemide and fludrocortisone test). The epidemiological impact of idRTA in the general population has not been assessed, due to the lack of biochemical signs and the difficulty in performing provocative tests.

However, multiple studies on urine acidification defects in patients presenting with urolithiasis indicate a prevalence of idRTA between 2% and 19% in this population of patients [60, 62–64]. It is reasonable to consider a formal acidification test in patients with unexplained stone disease, especially with recurrent or bilateral calcium–phosphate stones and hypocitraturia. Obviously, any patient with a urine pH <5.3 on a spontaneous urine sample does not need a formal acidification test. Moreover, a serum potassium level >3.8 mmol/L is reported to have a strong negative predictive value for idRTA [65].

It is not fully understood how idRTA can present without systemic acidosis, but reasons may include:

(i) Proton-buffering by phosphate released from the skeleton. In adults, the prevalence of idRTA in patients with idiopathic low BMD has been shown to be as high as 22% [66, 67]. This may also explain reports of the absence of overt acidosis in the AD form (*SLC4A1*) in early childhood, with subsequent development of systemic acidosis later on in life [4, 20, 68, 69].
(ii) Evidence of idRTA has been reported in carriers of variants in *ATP6V1B1* and in the heterozygous *Atp6v1b1* knock out mouse, consistent with a milder defect in acidification [70, 71].

The mechanisms of stone composition in idRTA are equivalent to those in the full forms: presence of alkaline urine and hypocitraturia favours calcium phosphate precipitation and the composition of this mineral can reach percentages as high as 100% [72]. In contrast to the full form, idRTA is not always associated with hypercalciuria [61].

The gold standard method for diagnosis is still considered to be urine acidification with oral ammonium chloride [19]; however, other alternatives like the furosemide and fludrocortisone (F + F) test have been described in more recent times particularly in views of the challenges with gastric tolerance of the former [73] (for details, see Supplementary data, Appendix 3: Procedures).

The treatment of patients with idRTA and recurrent stone disease is based on alkali supplementation [74]. Although no randomized controlled trials are available in the literature assessing the influence of alkali therapy on urolithiasis or mineral bone disease in idRTA, some small studies have shown that citrate can lead not only to reduced stone recurrence but also to improve bone health, hypercalciuria and citraturia [75] in adults, and growth in children [58].

Secondary forms of dRTA. Any patient with primary SS (pSS) and urolithiasis or hypokalaemia should be assessed for dRTA.

Primary (inherited) forms of dRTA present predominantly in childhood, although diagnosis may be delayed into adulthood in some patients with *SLC4A1*-associated disease [7]. Secondary forms typically present in adulthood and are most commonly associated with autoimmune disease, especially pSS [76]. Secondary dRTA can be complete or incomplete and has also been associated with medullary sponge kidney [77], nephrocalcinosis (including genetic causes of nephrocalcinosis, such as familial hypomagnesaemia with hypercalciuria and nephrocalcinosis [69, 78]) and drug toxicity among others. A list of conditions that have been associated with secondary dRTA is provided in Supplementary data, Table S1.

Criteria for diagnosis of autoimmune dRTA. Autoimmune dRTA arises in the context of a chronic interstitial nephritis associated with autoimmune conditions; pSS is by far the most common associated disorder [79] (see Supplementary data, Appendix 4.1 for diagnostic criteria). Other reported conditions include systemic lupus erythematosus, primary biliary cirrhosis, autoimmune hepatitis and autoimmune thyroiditis [80–83]. pSS-associated dRTA has been reported in 10–30% of cases [76, 84],

but often is incomplete and may be missed unless specifically looked for. Autoimmune dRTA has been associated with the presence of auto-antibodies against antigens on A-type intercalated cells [85]. When present, the dRTA may be 'complete' or 'incomplete'. If incomplete, a urinary acidification test (see the 'Secondary forms of dRTA' section) can be used to assess for an acidification defect.

Treatment

We recommend using alkali supplementation for the treatment of dRTA.

dRTA is a treatable disease and biochemical and clinical abnormalities associated with acidosis can be reversed or halted with adequate alkali supplementation.

Targets for treatment. We recommend maintaining plasma HCO_3^-, Cl^- and K^+, as well as urinary calcium excretion within the age-appropriate normal range.

In normal physiology, excretion of acid by the kidneys matches the acid load and thus maintains overall homeostasis [86]. In dRTA, the acid load is balanced by alkali supplementation and sufficient treatment is indicated by normalization of biochemistries. This also allows normalization of growth (in children) and bone mineralization and prevents progression of nephrocalcinosis.

Forms of alkali supplementation. Numerous forms of alkali supplementation exist. In a recent international study of 340 patients with a clinical diagnosis of dRTA, over 30 different alkali preparations were used [11]. Predominantly, these can be separated by the accompanying cation (Na^+ versus K^+, occasionally also Mg^{++}) and the alkali (bicarbonate versus citrate), as well as by the formulation (liquid versus tablet versus powder versus granules). There are some considerations for the choice of alkali supplement:

- Use of K^+-containing alkali addresses the concomitant hypokalaemia.
- Na^+-containing alkali may worsen the hypercalciuria [87].
- Citrate is a pro-drug: it is metabolized in the liver to bicarbonate. This step may increase the half-life of the supplement.
- In liquid formulations, alkali is usually more concentrated in citrate-containing supplements (2–3 mEq/mL) than in those containing bicarbonate (1 mEq/mL), thereby reducing the volume of medication needed.
- Many patients find citrate-containing formulations unpalatable.
- Bicarbonate-containing supplements are often associated with gas production in the stomach (CO_2) and belching.

However, the first three considerations are theoretical with no solid evidence to support them. In the 2019 international study, no difference in the prevalence of hypercalciuria was seen between Na^+- and K^+-containing formulations [7].

In clinical practice, pragmatic considerations, such as local availability, affordability and palatability are most important to support effective treatment and adherence. If a Na^+-containing formulation is used, separate K^+ supplementation may be necessary to maintain normal plasma levels.

A long-acting microgranular formulation containing K^+-citrate and K^+-bicarbonate was introduced in 2017 and has the potential advantages of reduced frequency of intake and better tolerability [88]. However, longer-term experience is lacking.

Dose and frequency of alkali administration. Dosage and frequency of alkali supplementation depend on the age of the patient, the biochemical response and pragmatic considerations. A usual starting dose is 2–3 mEq/kg/day. However, due to the higher metabolic rate and associated higher protein intake, as well as acid generation from skeletal mineralization, infants and younger children have an increased acid load and the dose may need to be increased [28]. Doses in excess of 10 mEq/kg/day have been reported but this usually reduces to 2–3 mEq/kg/day in older children and adults [4, 7]. The total daily dose needed to control acidosis can vary considerably between individuals. Factors contributing to this variability include the underlying molecular basis, as well as diet (see below).

Administration should be as frequent as possible to ensure sustained control of the acidosis. With large, but infrequent doses, patients may become alkalotic shortly after the dose, leading to excretion of bicarbonate in the urine, so that the buffering capacity of the dose is reduced. Moreover, the resulting increase in urine pH may increase the risk of calcium phosphate precipitation. Once the buffering capacity has been exhausted, patients will become acidotic with all associated complications, such as calcium release from bone with consequent hypercalciuria, until the next dose becomes effective.

In infants, who receive frequent feedings, a small volume of alkali may be added to each feed. This will not only help to sustain control of the acidosis, but also minimize the taste of the supplement, which otherwise can affect adherence. In older children and adults, less frequent dosing (three to four times daily) is likely to help adherence and allows uninterrupted sleep. If the extended release formulation is used, twice daily administration is sufficient [88].

Initial dosage depends on the age and mode of presentation. In infants presenting with marked acidosis (HCO_3^- <15 mmol/L), we recommend a starting dose of around 5 mEq/kg/day of alkali. 'Trough' (obtained directly before the next dose is due) plasma HCO_3^- levels should be checked every 24–48 h and the dose adjusted accordingly, until a stable normal plasma HCO_3^- level has been reached.

For infants identified by family screening but with normal HCO_3^- level, a starting dose of 1–2 mEq/kg/day is likely sufficient.

For children presenting beyond infancy, we recommend a starting dose of 2–3 mEq/kg/day.

In adults, a reasonable starting dose is 60 mEq/day of alkali with an increase in dosage by 15–20 mEq every 1–2 weeks until biochemical parameters have normalized.

K^+ supplementation. We recommend providing additional K^+ supplementation in patients with persistent hypokalaemia, yet well-controlled acidosis.

Severe hypokalaemia in dRTA has been associated with complications, such as paralysis (see the 'Hypokalaemia' section). The advantage of using K^+-alkali salts for supplementation is that they contain both K^+ and alkali and thus help normalize both the plasma potassium and bicarbonate levels. However, as a key presumed mechanism of hypokalaemia is avid Na^+ reabsorption in the collecting duct in exchange for potassium secretion (as protons are not available), supplementation with Na^+-alkali salts is expected to also improve K^+ levels.

Various formulations of KCl are available; these frequently cause dyspepsia and are recommended to be taken three to four times daily. Liquid potassium aspartate may be better tolerated than additional KCl and provides additional alkali.

Nutrition. We recommend informing patients of the effects of diet on acid load and alkali supplementation.

The acid load is almost completely derived from the sulphur-containing amino acids cysteine and methionine [89]. Of note, animal proteins contain a higher percentage of these sulphuric acid-generating amino acids than plant proteins [90]. In contrast, organic anions in fruits and some vegetables provide an alkali load [90]. Therefore, patients with a vegan diet may need less alkali supplementation than those with a high animal protein intake. While care must be taken especially in children to ensure the diet matches the recommended daily intake for protein to ensure sufficient growth, a diet avoiding excessive protein intake and rich in fruits and vegetables will minimize the acid load and thus can help reduce the need for alkali supplementation [89]. While patients should be free to determine their diet, nutritional information empowers them to take some control of their disease independent of prescribed medications.

Thiazides. We do not recommend the use of thiazides in the routine treatment of patients with dRTA.

Thiazides are commonly used to reduce urinary calcium excretion and for this reason are sometimes used also in dRTA. However, several important aspects should be considered:

- There are no solid data documenting the efficacy of thiazides in reducing urinary calcium excretion in dRTA.
- Hypercalciuria in dRTA reflects the effects of acidosis and therefore normalizes with adequate alkali supplementation.
- Indeed, urinary calcium excretion is commonly used as key indicator of adequate treatment and this could be lost, if affected by thiazide treatment.
- Thiazide use is associated with hypokalaemia, which can aggravate the hypokalaemia of dRTA. While this can be controlled with the addition of a K^+-sparing diuretic or increased K^+ supplementation, this will further increase the medication burden.

Follow-up and long-term outcome. We recommend that patients with dRTA are regularly assessed, clinically and biochemically (Table 2).

Few long-term outcome data are available for dRTA and these may be skewed by the fact that current older adults may have not received optimal therapy in early childhood. Nevertheless, available data suggest that early diagnosis and adequate metabolic control improve long-term outcome with respect to final height and estimated glomerular filtration rate (eGFR), highlighting the importance of regular monitoring of treatment adequacy [7]. Recommended parameters for monitoring are detailed in Table 3. Frequency of follow-up depends on the age and stability of plasma HCO_3^- levels: in infants, follow-up every 1–3 months may help to ensure adequate control of the acidosis by adjustment of dose to the growth of the patient. In older, stable children, follow-up every 6 months may be sufficient. Adults with stable disease and eGFR may do well with annual follow-up. For those with more active stone disease, more frequent follow-up may be desirable, for example 3–4 monthly. A more frequent follow-up schedule is warranted in the titration phase of alkali supplementation [49]. Those with advanced CKD also may benefit from more frequent follow-up as per KDIGO [91] or local guidelines. In patients with autoimmune dRTA who are on systemic immunosuppression frequency of follow-up is typically dictated by the monitoring and titration of the immunosuppression.

Imaging. We recommend that all patients have a urinary tract ultrasound performed at diagnosis and in regular intervals at follow-up.

Nephrocalcinosis and nephrolithiasis are common complications of dRTA and monitoring is recommended to facilitate early detection of stones for consideration of measures to prevent urinary obstruction. Unless there is an acute reason to perform imaging studies, it is reasonable to have surveillance imaging once every 1–2 years. This could be a renal tract ultrasound, which involves no radiation, or computed tomography (CT) scanning, which is the gold standard for imaging calcium. Ultra-low dose CT protocols have recently shown similar performance to classical CT imaging on the detection of stones in the urinary tract, with considerably lower radiation exposure [92], and therefore may be preferred.

Over time, patients may develop kidney cysts, typically in the medulla. The aetiology of these is unclear.

Secondary and tertiary care. We recommend that a tertiary care centre with experience in the diagnosis and treatment of dRTA should be involved in the care of patients with dRTA.

Since dRTA is a rare disease and inadequate treatment associated with poorer long-term outcome, patients should have access to tertiary care centres with experience in dRTA management. This is to facilitate clinical and genetic diagnosis, optimize treatment and patient education, as well as access to specialist stone urology, if needed.

For patients who live far from a specialist centre, follow-up can be shared with a local nephrologist and urologist.

CONCLUSION

The clinical practice points (summarized in Table 4) reflect the expert consensus opinion of the authors. We recognize that currently there is little or insufficient evidence to fully support these. These practice points are to establish an initial standard for the management of dRTA and to facilitate collection of

Table 4. Summary of recommendations

Indication	Recommendation
For diagnosis	In a patient with symptoms suggestive of dRTA (Table 1), we recommend to obtain comprehensive clinical, biochemical and radiological information (Table 2) to ascertain the underlying diagnosis
	We recommend offering genetic testing to all patients with a clinical suspicion of primary dRTA
	We recommend that a negative genetic test should prompt a careful review of clinical features to confirm the correct clinical diagnosis, as well as analysis of the relevant genes for the differential diagnosis
	We do not recommend routine assessment of bone mineralization by methods such as X-rays and DEXA in children with dRTA
	In adults, assessment of BMD by DEXA every 2–3 years may be helpful in assessing fracture risk and treatment adequacy
	We recommend to assess urinary acidification in patients with nephrocalcinosis/nephrolithiasis and borderline low plasma bicarbonate levels
	Any patient with pSS and urolithiasis or hypokalaemia should be assessed for dRTA
For treatment and follow-up	We recommend using alkali supplementation for the treatment of dRTA
	We recommend maintaining plasma HCO_3^-, Cl^- and K^+, as well as urinary calcium excretion within the age-appropriate normal range
	We recommend providing additional K^+ supplementation in patients with persistent hypokalaemia, yet well-controlled acidosis
	We recommend informing patients of the effects of diet on acid load and alkali supplementation
	We do not recommend the use of thiazides in the routine treatment of patients with dRTA
	We do not recommend the use of growth hormone in children with dRTA, unless there is persistent growth retardation despite adequate metabolic control
	We recommend that patients with dRTA are regularly assessed, clinically and biochemically
	We recommend that all patients have a renal tract ultrasound performed at diagnosis and in regular intervals at follow-up
	We recommend that a tertiary care centre with experience in the diagnosis and treatment of dRTA should be involved in the care of patients with dRTA
	For recessive dRTA linked to ATP6V1B1, ATP6V0A4 or FOXI1, we recommend early and developmentally appropriate hearing screening. In addition, all patients at risk should have at least one diagnostic audiology assessment by 24–30 months of age. Patients with sensorineural hearing loss should have appropriate audiological follow-up
	There is currently insufficient evidence to recommend that children with inherited dRTA related to genetic defects other than WDR72 should undergo a specific dental assessment for AI

long-term data. As more evidence emerges, we fully expect that our recommendations will need updating.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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CONFLICT OF INTEREST STATEMENT

All authors declare that there is no conflict of interest.

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