

# Diagnosis and Management of Bartter syndrome: Consensus and Recommendations from the ERKNet Working Group for Tubular Disorders

Martin Konrad<sup>1</sup>, Tom Nijenhuis<sup>2</sup>, Gema Ariceta<sup>3</sup>, Aurelia Bertholet-Thomas<sup>4</sup>, Lorenzo A. Calo<sup>5</sup>,  
Giovambattista Capasso<sup>6</sup>, Francesco Emma<sup>7</sup>, Karl Peter Schlingmann<sup>1</sup>, Mandeep Singh<sup>8</sup>, Francesco Trepiccione<sup>6</sup>,  
Stephen B. Walsh<sup>9</sup>, Kirsty Whitton<sup>10</sup>, Rosa Vargas-Poussou<sup>11</sup>, Detlef Bockenhauer<sup>9,12</sup>

<sup>1</sup>Department of General Pediatrics, University Hospital Münster, Germany

<sup>2</sup>Department of Nephrology, Radboud University Medical Center, Nijmegen, the Netherlands

<sup>3</sup>Pediatric Nephrology, Hospital Universitari Vall d' Hebron, Universitat Autònoma de Barcelona, Spain

<sup>4</sup>Université Claude Bernard Lyon 1, Lyon, France

<sup>5</sup>Department of Medicine (DIMED), Nephrology, Dialysis, Transplantation, University of Padova, Italy

<sup>6</sup>Division of Nephrology, Department of Translational Medical Sciences, School of Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy

<sup>7</sup>Division of Nephrology, Department of Pediatric Subspecialties, Bambino Gesù Children's Hospital IRCCS, Rome, Italy

<sup>8</sup>Fetal Medicine Centre, Southend University Hospital NHS Foundation Trust, Essex, United Kingdom.

<sup>9</sup>UCL, Department of Renal Medicine, London, UK

<sup>10</sup>London, UK

<sup>11</sup>Hôpital Européen Georges Pompidou, Assistance Publique Hôpitaux de Paris, Centre d'Investigation Clinique, Paris, France; Centre de Référence des Maladies Rénales Héritaires de l'Enfant et de

l'Adulte, Paris, France

<sup>12</sup>Department of Pediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH, UK

*Corresponding author:* Martin Konrad, [konradma@uni-muenster.de](mailto:konradma@uni-muenster.de)

**Abstract** Bartter syndrome is a rare inherited salt-losing renal tubular disorder characterized by secondary hyperaldosteronism with hypokalemic and hypochloremic metabolic alkalosis and low to normal blood pressure. The primary pathogenic mechanism is a defective salt reabsorption in the distal part of the nephron, especially in the thick ascending limb of the loop of Henle. Patients present with significant variability in the clinical expression of the disease, which is genetically heterogeneous with 5 different genes described to date. Despite considerable phenotypic overlap, correlations of specific clinical characteristics with the underlying molecular defects have been demonstrated, generating typical gene-specific phenotypes. As with many other rare disease conditions, there is a paucity of clinical studies that could guide diagnosis and therapeutic interventions. In this expert consensus document, the authors have summarized the currently available knowledge, propose clinical indicators to assess and improve quality of care, and highlight open questions for future research.

## I. INTRODUCTION

The term Bartter syndrome (BS) encompasses different inherited salt-losing tubulopathies characterized by polyuria, hypokalemia, hypochloremic metabolic alkalosis, and normotensive hyperreninemic hyperaldosteronism. Five different forms have been identified to date, based on molecular genetics (table 1)<sup>1</sup>.

Clinical characteristics, such as severity of biochemical abnormalities, presence of polyhydramnios and preterm delivery, the degree of calciuria with or without medullary nephrocalcinosis, and presence of sensorineural deafness show typical gene-specific patterns. Several patients with BS type 3 have features that are virtually indistinguishable from Gitelman syndrome (GS), another salt-losing tubulopathy<sup>1</sup>.

The exact incidence and prevalence of BS is unknown. Based on rough estimates, an annual incidence of 1:1.000.000 has been proposed<sup>2</sup>. More precise calculations based on the carrier state prevalence for *SLC12A1* and *KCNJ1* mutations in the Framingham Heart Study indicate a prevalence of 1:100.000 for these two types of BS<sup>3</sup>. Thus, the overall prevalence of all types of BS (1-5) in Western countries is probably close to 1:40.000-50.000.

The primary molecular defect in all types of BS leads to an impaired salt reabsorption in the thick ascending limb (TAL) of Henle's loop<sup>4</sup>. The clinical consequences that are observed in patients with BS can be compared with chronic administration of loop diuretics (e.g. furosemide), in contrast to those observed in patients with GS who resemble chronic thiazide administration<sup>5</sup>. Irrespective of the underlying molecular defect, mutations result in renal tubular salt wasting with activation of the renin-angiotensin system (RAS) with consequent hypokalemic and hypochloremic metabolic alkalosis. In addition, the tubuloglomerular feedback is altered at the level of the macula densa, which, under physiologic conditions, senses low tubular chloride concentrations in conditions of volume contraction. This activates cyclooxygenases

(primarily COX-2) to produce high amounts of prostaglandins (primarily PGE<sub>2</sub>) that in turn stimulate renin secretion and aldosterone production, in the attempt of reestablishing normal intravascular volume and glomerular perfusion<sup>6</sup>. In BS, the tubuloglomerular feedback is uncoupled because chloride is not reabsorbed in the macula densa due to the underlying molecular defects. Therefore, cells produce high amounts of PGE<sub>2</sub> irrespective of volume status, causing excessive synthesis of renin and aldosterone. This constitutes the rationale for treating BS patients with prostaglandin synthesis inhibitors, such as indomethacin, ibuprofen or specific COX-2 inhibitors (e.g. celecoxib), which often result in noticeable clinical improvement<sup>7-9</sup>. Excessive stimulation of macula densa cells explains the characteristic hyperplasia of the juxtaglomerular apparatus that was already described in Bartter's original report<sup>10</sup>.

While hyperaldosteronism causes hypokalemic metabolic alkalosis, volume depletion explains, at least in part, arterial hypotension. In addition, PGE<sub>2</sub> has vasodilatory effects, which may contribute to low blood pressure<sup>8</sup>. Interestingly, heterozygous carriers of BS mutations have, on average, lower blood pressure, compared to control subjects<sup>3</sup>.

Impaired salt reabsorption in the TAL has two additional consequences that are important in BS, namely

- I. a reduction of calcium reabsorption in the TAL, where calcium (and magnesium) is reabsorbed through paracellular pathways that are dependent on the transepithelial electrochemical potential, which is generated by the concerted action of the NKCC2 and KCNJ1 (also called ROMK or Kir1.1) proteins. Consequently, patients have hypercalciuria and develop progressive medullary nephrocalcinosis<sup>11,12</sup>, and
- II. a reduction or complete blunting of the osmotic gradient in the renal medulla, causing isosthenuria, i.e. an impaired ability to dilute or concentrate the urine<sup>13</sup>.

An exception are most patients with BS3 who have a milder defect without hypercalciuria and partial capacity to concentrate the urine.

To date 5 different causative genes have been identified (table 1, figure 1). The mode of inheritance is autosomal recessive in BS type 1-4 and X-linked recessive in BS type 5. The first one was *SLC12A1*, encoding the Na-K-2Cl cotransporter (NKCC2), the target of loop diuretics, expressed in the TAL (BS1)<sup>14</sup>. Potassium entering the cell via this cotransporter recycles through the apical potassium channel KCNJ1, the encoding gene *KCNJ1* constituting the 2<sup>nd</sup> causative gene (BS2)<sup>15</sup>.

Chloride reabsorbed via NKCC2 exits the cell on the basolateral side predominantly through the chloride channel ClC-Kb, encoded by *CLCNKB*, the 3<sup>rd</sup> causative gene for BS (BS3)<sup>16</sup>. Barttin is a necessary subunit for ClC-Kb and is encoded by *BSND*, the 4<sup>th</sup> causative gene (BS4a).<sup>17,18</sup>

Barttin is also a necessary subunit for the chloride channel ClC-Ka and the phenotype of BS4 can be mimicked by combined recessive mutations in *CLCNKB* and *CLCNKA* (BS4b), suggesting that the ClC-Ka protein contributes to the basolateral chloride conductance in the TAL<sup>19</sup>. Milder forms of type 4a BS have also been described; they are caused by missense mutations that presumably allow residual function of the Barttin protein<sup>20-22</sup>.

Lastly, mutations in *MAGED2* have been identified in a very severe antenatal form of BS, which resolves spontaneously during the first weeks to months of life<sup>23</sup>. BS type 5 inheritance is X-linked recessive and therefore the vast majority of patients are males.

Few cases of Bartter-like phenotypes developing during childhood with gain of function mutations in the calcium sensing receptor (CaSR) have been described; these patients have a diagnosis of autosomal dominant hypocalcemia (OMIM#601198)<sup>24</sup>. They were sometimes previously indicated as "BS type 5", but this designation has been abandoned, and the term BS type 5 refers to X-linked transient BS, in accordance with the current OMIM nomenclature.

Renal tubular salt-wasting associated with hypokalemic metabolic alkalosis is highly suggestive of BS. The most frequent clinical symptoms are polyuria, dehydration, failure to thrive, growth retardation and a past medical history of polyhydramnios with premature birth. Renal salt loss is frequently associated with hypercalciuria and nephrocalcinosis. BS is a potentially life-threatening condition that necessitates a rapid diagnosis and therapy.

Most patients with BS receive supplementation with sodium chloride, potassium chloride and fluids that are adjusted individually based on symptoms, tolerability, severity of the tubulopathy, age of the patient and GFR. In addition, non-steroidal anti-inflammatory drugs (NSAIDs) are for most patients a mainstay of treatment<sup>25</sup>, at least during the first years of life (except transient BS5). The use of other therapies, such as potassium-sparing diuretics, angiotensin converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs) have been reported to the literature, but evidence supporting their efficacy, tolerability and safety are limited.

Despite significant gain in knowledge since the genetic elucidation of these diseases, information on long-term outcome of BS is almost completely lacking. In particular, the risk of chronic renal failure and its potential relation to prolonged use of NSAIDs, chronic hypokalemia, and chronic hypovolemia is not well documented. Likewise, little information exists on the incidence of secondary hypertension and of cardiac arrhythmias. Other open questions include optimal diagnostic approaches, in particular in the neonatal period, and the best therapeutic strategies based on outcome data. Most women with BS are fertile, but the best management of BS during pregnancy has not been established.

To begin addressing these questions, an interdisciplinary group of experts including pediatric and adult nephrologists, geneticists, obstetricians and patient representatives was assembled under the umbrella of ERKNet, the European Reference Network for Rare Kidney Diseases. This report summarizes their conclusions, provides guidance for managing these patients and highlights important points for future research. These recommendations are endorsed by the European Society for Paediatric Nephrology (ESPN) and the Working Group on Inherited Kidney Disorders (WGIKD) of the European Renal Association - European Dialysis and Transplantation Association (ERA-EDTA).

## II. METHODS

The consensus process was initiated by the European Rare Kidney Disease Reference Network (ERKNet). In addition to pediatric and adult nephrologists and geneticists, external experts in gynecology/obstetrics and patient representatives were invited to participate. Two groups were assembled: a consensus core group and a voting panel. The core group comprised specialists for pediatric (G.A., D.B., F.E., M.K., K.P.S.) and adult nephrology (A.B.T., L.C., G.C., T.N., F.T., S.W.), genetics (R.V.P.), obstetrics (M.S.) and a patient representative (K.W.). The voting group included 36 members with expertise in pediatric and adult Bartter syndrome, including members of the supporting societies and networks).

Supported by the ERKNet staff, the core group performed a systematic literature review in advance of the 1<sup>st</sup> consensus conference held on Nov 19<sup>th</sup> 2018 in Frankfurt/Main, Germany. The PubMed and Cochrane databases were searched until Oct 15<sup>th</sup> 2018; all articles and reports were considered, including randomized controlled trials, uncontrolled or observational studies, registries, summaries and case reports, restricted to human studies in English. The following key MeSH terms were used: Bartter syndrome, inherited hypokalemic alkalosis, SLC12A1, KCNJ1, CLCNKA, CLCNKB, BSND, MAGED2. The search retrieved 2218 results and 135 articles were referenced here.

Initial recommendations were developed during the first conference by discussion in thematic workgroups and plenary sessions. Evidence and recommendations were graded (whenever possible) according to the method used in the current American Academy of Pediatrics (AAP) guidelines<sup>26,27</sup>. The grading of recommendations into strong, moderate and weak takes into account not only the quality of evidence but also the balance of potential benefits and harms (Fig. 2) assessed by the consensus core group<sup>26</sup>. A first written draft was compiled by D.B., F.E. and M.K. and reviewed by all members of the consensus core group. Remaining gaps were identified by a second meeting held on May 16<sup>th</sup> 2019 in Heidelberg, Germany. Consequently, two rounds of anonymous voting were performed using the Delphi method until at least 70% support was reached for each individual recommendation. The voting group included all members of the consensus core group, members of the ERKNet expert group for tubulopathies, members of the ERA-EDTA WGKID, all having special expertise in Bartter syndrome. Failing a 70% level of consensus, recommendations were modified after discussion in the core consensus group and reviewed again by the voting panel until a consensus level of at least 70% was achieved.

## III. Diagnosis

### *General approach*

The diagnosis of BS is primarily based on clinical, biochemical and sonographic findings (Box 1, Recommendations for diagnosis). Even if the different subtypes of BS can usually be characterized clinically (table 2), we recommend genetic analysis after the confirmation of clinical suspicion.

### Antenatal diagnostic work-up

During pregnancy, the detection of early polyhydramnios of fetal origin typically around 28-32 weeks gestation should raise the

clinical suspicion of BS. In principle, there are two possible options to confirm the diagnosis: (i) prenatal genetic testing, and (ii) biochemical analysis of amniotic fluid. Both measures are invasive and carry the risk of procedure-related complications. But there may be clinical situations where the establishment of a confirmed diagnosis of BS is helpful for counseling of the couple and discussion of possible therapeutic measures.

Whenever there is a need for prenatal diagnosis, we consider genetic testing the most reliable method, although approximately 25% of patients with a clinical diagnosis of BS do not have genetic confirmation<sup>28</sup>. In situations, where genetic testing is not available or diagnostic, the assessment of the “Bartter index” may be considered as an alternative way to confirm the diagnosis of BS in utero. In the past, anecdotal reports indicated the possibility of diagnosing BS by measuring electrolytes (high chloride) and/or aldosterone in the amniotic fluid<sup>29,30</sup>. However, a larger study including 36 cases of polyhydramnios secondary to BS failed to show differences in aldosterone concentrations<sup>31</sup>. Likewise, another study found no significant differences in sodium, chloride or potassium concentrations between amniotic fluid from BS-related polyhydramnios, polyhydramnios from other causes or control pregnancies. This same study found significant differences in total protein and alfa-fetoprotein content, and developed a “Bartter index” that had a 93% sensitivity and 100% specificity<sup>32</sup>. In a subsequent study including 464 pregnancies of which 28 were complicated by fetal BS, these results were largely confirmed with 86% sensitivity and 84% specificity. Of note, in three of the four patients that were not correctly diagnosed with BS, samples were obtained at 23 weeks of gestation and in one case from a woman under indomethacin therapy<sup>33</sup>.

### Postnatal diagnostic work-up

The diagnostic work-up for BS after birth should include a detailed clinical evaluation including a family history of pregnancy complicated by polyhydramnios with/without premature birth, and a past medical history of polyuria, episodes of dehydration, unexplained fever, failure to thrive and recurrent vomiting. In children, growth charts are very helpful to assess the development of height and weight. Additional clinical signs may include salt craving (does the child prefer a sweet or savoury treat?), muscle weakness, low blood pressure, and pubertal delay.

Laboratory analysis for suspected BS should include measuring renal function, serum electrolytes (including magnesium), acid-base status, serum renin and aldosterone levels, calculation of the fractional excretion of chloride (usually >1%), urinary calcium excretion (the calcium/creatinine ratio from spot urine is appropriate, for age specific reference values see table 3), and renal ultrasound. The assessment of urinary prostaglandin excretion (PGE<sub>2</sub>) may be helpful, however, this needs laboratory expertise and a cooled 24-h-urine. Thus, this procedure is not feasible in a routine clinical setting. For definitive diagnosis, we recommend genetic testing when the clinical suspicion is confirmed.

### *Clinical characteristics of different types of BS (table 2)*

In the following section, we highlight the key clinical and biochemical findings in patients with BS with a special focus on the gene-specific differences between the known subtypes of BS. For differential diagnosis, please see below (section 4).

### Age at presentation

BS is a severe and potentially life-threatening condition causing polyhydramnios and premature birth in the majority of patients. Polyhydramnios develops between the 20<sup>th</sup> and the 30<sup>th</sup> week of gestation, secondary to fetal polyuria. The timing and severity vary according to the type of mutations. In patients with mutations in *BSND* or *MAGED2* (BS4 and 5), polyhydramnios is usually observed very early, compared to BS1 and 2<sup>23,34-36</sup>. Patients with BS3 usually become symptomatic later in life. Nonetheless, a prenatal presentation does not exclude BS3. Up to 25% of patients develop polyhydramnios during pregnancy, although rarely associated with amniotic drainage or premature birth<sup>37</sup>. BS5 always has antenatal presentation, but symptoms spontaneously resolve typically around the estimated date of delivery.

Although postnatal onset of symptoms has been described in very few cases of BS1 and 2, the vast majority of patients with clinical onset beyond infancy have BS3. Pooled data from different studies including more than 270 patients indicate that patients with BS3 are diagnosed after the age of 1 year in 50-70% of cases<sup>37-43</sup>. Symptoms are nonspecific and also common to other salt-losing tubulopathies. Patients typically present with failure to thrive, poor weight gain or polyuria with polydipsia<sup>37,39,43</sup>. Less frequent symptoms are related to dehydration including constipation, permanent thirst, unexplained fever, hyponatremia and recurrent vomiting. Most patients exhibit salt craving, although this is rarely a presenting symptom. In a minority of cases, the diagnosis is made after noticing abnormal laboratory results, in particular hypokalemia, metabolic alkalosis, and hypochloremia<sup>38-42</sup>, after accidental discovery of nephrocalcinosis<sup>37-44</sup>, or by screening for positive family history.

### Salt wasting, plasma potassium, chloride, magnesium and bicarbonate levels

After birth, the first clinical sign of renal salt loss is the rapid development of massive polyuria (often exceeding 10 ml/kg/h). In most cases, polyuria is present at birth and causes rapid weight loss (often apparent at day 1) and clinical signs of dehydration. Hypochloremic and hypokalemic metabolic alkalosis may not be present during the first days of life, especially if patients experience acute kidney injury from dehydration. Moreover, infants with BS2 often have transient hyperkalemia after birth because loss of function mutations in the *KCNJ1* channel also impair potassium secretion along the collecting duct<sup>39,45</sup>. Hyperkalemia in BS2 disappears over time most likely because of the developing expression of alternative potassium channels (most likely *MAXI-K* channels) in this part of the nephron compensating for the lack of *KCNJ1* activity. Nevertheless, on average, plasma potassium levels remain higher in BS2, which together with the initial hyperkalemia can be used as a distinguishing feature. In contrast, patients with BS3 and 4 tend to have the lowest plasma chloride levels and the most pronounced alkalosis. This can also be captured by a low plasma chloride-sodium ratio<sup>37</sup>. Interestingly, this ratio tends to be increased in BS5<sup>36</sup> (table 2). In some patients with BS3, hypomagnesemia may be present.

### Calciuria and nephrocalcinosis

Hypercalciuria is a typical feature of BS1 and 2. However, at birth, renal ultrasound does not show nephrocalcinosis and prenatal nephrocalcinosis has never been reported in BS. No precise data

are available on the time course of nephrocalcinosis. It is often detected after 1-2 months of life in patients with BS1 and 2. While a CT scan provides more accurate assessment of renal calcifications than renal ultrasound, it is associated with radiation burden, and thus should be reserved for clinical situations, where there is a direct therapeutic consequence, e.g. localization of stones in obstructive uropathy that may occur in rare cases in BS.

In contrast, patients with BS3 and 4 usually have normocalciuria, although hypercalciuria has been described in some. Interestingly, hypocalciuria has also been reported in patients with BS3 and these patients mimic the phenotype of GS. It is important to note that calcium excretion in BS3 may differ between patients from the same family all having the same mutations and may even change over time in an individual patient<sup>46,47</sup>. This phenotypic overlap is best explained by impairment of salt reabsorption also in the DCT, where *CIC-Kb* is normally expressed. Studies indeed show that mean urinary calcium/creatinine ratios are lower in GS, but with considerable overlap with BS3, as is the case for serum magnesium<sup>37,40,43</sup>.

In BS5, hypercalciuria may be observed but due to the transient nature of the disease nephrocalcinosis is a rare finding<sup>23,36</sup>.

### Genetic testing

The detection of bi-allelic inactivating mutations in one or more (BS4b) of the 5 genes responsible for recessive forms of BS or a hemizygous mutation in *MAGED2* responsible for the X-linked transient form (BS5) is crucial to confirm the diagnosis of BS and for genetic counselling (table 1).

The analytical sensitivity (likelihood that the assay will detect a sequence variant when present within the targeted region) and specificity (likelihood that the assay will be negative when no variant is present) of current genetic tests for BS is 90% to 100% and 100%, respectively. Because there are BS patients with recessive forms who do not have two identifiable mutations, the clinical sensitivity (proportion of positive tests if the disease is present) is about 75%<sup>36,39</sup>. However, this depends on age at diagnosis: whereas sensitivity was 75% in a large pediatric cohort<sup>28</sup>, this decreased to 12.5% in adult patients<sup>48</sup>. This difference is possibly related to the broader differential diagnosis (especially abuse of diuretics and laxatives) in adults and the higher proportion of patients with BS3 since the analysis of *CLCNKB* is technically challenging. Although large rearrangements (deletions or duplications) can be detected by Next Generation Sequencing (NGS), it is recommended to confirm them by a second independent method (e.g. multiplex ligation-dependent probe amplification or quantitative PCR). Large rearrangements are particularly frequent in the *CLCNKB* gene but have also been described in *KCNJ1*, *BSND* and *MAGED2*<sup>17,36,49</sup>.

As genetic testing becomes more accessible and comprehensive, we recommend offering it to all patients with a clinical suspicion of BS. It should be performed in a laboratory accredited for diagnostic genetic testing. Especially the analysis of the *CLCNKB* gene needs special expertise (amplification and variant interpretation) because of the high sequence homology with the neighbouring *CLCNKA* gene. Taking into account the genetic heterogeneity, the use of a gene panel for parallel sequencing of all genes (in 1 test) is recommended; this should include also the relevant genes for the differential diagnosis of BS. At present, different gene panels are available; they should at least include the *SLC12A1*, *KCNJ1*,

*BSND*, *CLCNKA*, *CLCNKB*, *MAGED2* and *SLC12A3* genes. For extended differential diagnosis we suggest to include genes responsible for congenital chloride diarrhoea (*SLC26A3*), HELIX syndrome (*CLDN10*), EAST/SeSAME syndrome (*KCNJ10*), and autosomal dominant hypocalcemia (*CASR*); for suspected BS2 also the genes for type 1 pseudohypoaldosteronism (*NR3C2*, *SCNNIA*, *SCNNIB* and *SCNNIG*) should be included. In atypical cases, the genes defective in hypervolemic hypokalemic alkalosis (apparent mineralocorticoid excess (*HSD11B2*); Liddle syndrome (*SCNNIA*, *SCNNIB* and *SCNNIG*), glucocorticoid-remediable hyperaldosteronism (chimeric *CYP11B1/CYP11B2*) need to be considered. If Sanger sequencing is the only available technique in the diagnostic laboratory, sequential testing of the candidate genes according to the clinical phenotype is recommended.

If only a single variant has been identified by panel analysis or conventional sequencing, the analysis should be complemented with a test for a deletion (multiplex ligation-dependent probe amplification) on the other allele.

It must be kept in mind that in 5% to 15% of patients<sup>37,39</sup> even after searching for large rearrangements, no or only one heterozygous pathogenic mutation is discovered. In these cases, mutations in regulatory regions including introns or in another, yet unidentified disease gene might be causative. Nevertheless, a negative genetic test should prompt a careful review of clinical features to confirm the correct clinical 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 unknown significance could be confirmed as pathogenic. Diagnostic laboratories should consult the evolving databases and consider *in vitro* studies to interpret patient results appropriately.

An early genetic diagnosis for a patient with BS allows an accurate diagnosis and treatment, resolving difficult cases with overlapping phenotypes and reclassifying the disease. The main differential diagnosis of BS in the neonatal period includes congenital chloride diarrhoea and type 1 pseudohypoaldosteronism (similar phenotype to BS2 with hyperkalemia), which have different treatments and complications. In addition, the identification of the genetic defect may prompt screening for and treatment of deafness in patients with BS4 and for avoiding aggressive treatments and explaining the transient character in patients with BS5.

Genetic counselling should be offered to any patient with BS and to parents with a child suffering from the disease. This counselling could help discuss testing parents, siblings and partner. Testing relatives is particularly useful to identify heterozygous female carriers in families with an index case carrying a *MAGED2* mutation. Prenatal diagnosis and preimplantation genetic diagnosis are technically feasible after reliable genetic counselling and may be considered on an individual basis, according to national ethical and legal standards. Prenatal diagnosis also facilitates a well-timed "*in utero* transport" to a tertiary perinatal unit.

#### IV. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of BS highly depends on the age at presentation and the specific context (table 4).

Data comparing the gestational age at onset of polyhydramnios in different fetal conditions are scarce. Current evidence indicates that the severity of polyhydramnios is predictive of a serious fetal disease including BS<sup>50,51</sup>. The risk is 10-fold higher if polyhydramnios is severe, as defined by an amniotic fluid index >35 cm. All polyhydramnios secondary to BS reported to date (except BS3) fall in this category with amniotic fluid indices exceeding the 35 cm threshold<sup>23,36</sup>.

Polyhydramnios due to excessive fetal polyuria is virtually always caused by BS. There are no reports of inherited tubular disorders other than BS causing severe polyhydramnios secondary to fetal polyuria. In particular, polyhydramnios is neither a feature in severe proximal tubulopathies nor in nephrogenic diabetes insipidus. There are reports of polyhydramnios in infants misdiagnosed with pseudohypoaldosteronism type I, but these cases have later been shown to harbour *KCNJ1* mutations<sup>39,45</sup>.

Congenital chloride diarrhoea can be confused with BS. Postnatally, this disease causes pronounced metabolic alkalosis secondary to watery diarrhoea, and pregnancies are often complicated by polyhydramnios with preterm delivery (usually not severe)<sup>52</sup>. It is important to note that chloride loss in these infants is intestinal and biochemical analysis of the urine will reveal minimal chloride content. However, due to the watery consistency of the stool, it can be easily confused with urine and a catheter specimen may be necessary. Dilated intestinal loops are frequently observed by ultrasound from the end of the second trimester of pregnancy onwards and should raise suspicion of this diagnosis.

The differential diagnosis in the postnatal period and in infancy further includes "pseudo-Bartter syndrome" as occasionally observed in cystic fibrosis. Again, salt loss in this condition is extrarenal and analysis of urinary chloride excretion is helpful. In one review<sup>43</sup>, fractional excretion of chloride in BS was always >0.5%, despite the presence of volume and chloride depletion.

Beyond infancy, and especially if BS patients present in adolescence or even adulthood (most often BS3), the differential diagnosis can be challenging. GS is a primary consideration in those patients with hypocalciuria and/or hypomagnesemia. Patients with HNF1B nephropathy may also present with hypokalemic alkalosis<sup>53</sup>. Other very rare renal tubular disorders exhibiting metabolic alkalosis include HELIX syndrome (*CLDN10*)<sup>54,55</sup>, EAST syndrome (*KCNJ10*)<sup>56</sup>, and autosomal dominant hypocalcemia (*CASR*)<sup>24</sup>. Patients with apparent mineralocorticoid excess (AME) present with polyuria, hypokalemic hypochloremic alkalosis, hypercalciuria and nephrocalcinosis but can be distinguished from BS by the presence of volume excess with elevated blood pressure and suppressed renin and aldosterone levels<sup>57</sup>.

Some patients with BS primarily present with nephrocalcinosis and/or urolithiasis. A young age at onset of urinary stone disease should raise clinical suspicion of a specific underlying cause, including (incomplete) distal renal tubular acidosis (dRTA) and other inherited tubulopathies. These differential diagnostic considerations will prompt blood gas analysis and electrolyte evaluations. The presence of hypokalemic alkalosis will distinguish BS from proximal or distal forms of RTA which are characterised by hypokalemic acidosis.

When the presenting sign is hypokalemia, the initial differential diagnosis is wide. In this context, it is important to differentiate renal from gastrointestinal potassium loss and potassium shifts, primary hyperaldosteronism, and to exclude external causes

(drugs including loop and thiazide diuretics, chronic liquorice ingestion, acute treatment with salbutamol or other beta-agonists). When hypokalemic alkalosis is diagnosed and diuretic and/or laxative (ab)use is ruled out, the differential diagnosis narrows down to rare tubulopathies including Liddle's syndrome, apparent mineralocorticoid excess and the salt-wasting tubulopathies. In Liddle's syndrome, a gain-of-function mutation in the epithelial sodium channel ENaC causes a clinical phenotype resembling mineralocorticoid excess which, in contrast to BS and GS, includes hypertension and low renin and aldosterone levels. Other clinical features that generally argue against a diagnosis of BS include low renin, low fractional urinary chloride excretion (<0.5%) and low urinary potassium excretion.

Urinary chloride excretion assessed either by fractional chloride excretion or urinary sodium/chloride excretion is an informative tool to distinguish renal from extra-renal salt losses. Because of the critical importance of sodium for volume homeostasis, sodium excretion in steady state will mirror sodium intake, as a persistently negative sodium balance would lead to hypovolemia with consequent shock. In order to maximize sodium retention, sodium reabsorption in the collecting duct is upregulated, in exchange for potassium or proton secretion. This is the basis for the hypokalemic alkalosis. To maintain electro-neutrality, anions need to be excreted, including chloride.<sup>43,58</sup> In BS (as well as GS), fractional urine chloride excretion is elevated (>0.5%) and the urine sodium over chloride ratio is close to 1. In contrast, patients with gastrointestinal potassium loss have low urine chloride excretion rates. Because gastric secretions contain far more chloride than sodium, patients with e.g. bulimia have larger chloride than sodium losses from vomiting and thus excrete more sodium than chloride in their urine. A urine sodium/chloride ratio >1.6 is typical for these patients<sup>59</sup>. Patients with diarrhoea (except congenital chloride diarrhoea) and surreptitious laxative use can lose large amounts of potassium and sodium in the stool, accompanied by a relatively small amount of chloride. In addition, the loss of stool bicarbonate and ensuing hypokalemia can stimulate renal tubular acid or ammonium secretion with accompanying chloride excretion. Therefore, a low urine sodium/chloride ratio <0.7 ensues. Patients with surreptitious diuretic use display highly variable urine sodium and chloride excretion, but with a fixed urinary sodium/chloride ratio similar to that in BS.

The function of specific renal tubular segments can be clinically tested by e.g. administering specific drugs (diuretics, antidiuretic hormone) and by water, salt or acid loading. Classical examples include synthetic antidiuretic hormone (DDAVP) testing in nephrogenic diabetes insipidus, clearance of free water in BS, and thiazide testing in GS. However, we do not recommend performing such tubular function tests routinely in BS.

Firstly, performing tubular function tests does not appear relevant in infancy, when the clinical phenotype is often readily apparent. In addition, there is a potential risk of severe volume depletion in subjects with suspected BS because they are at risk of an exaggerated response to thiazides due to the compensatory upregulation of salt reabsorption in the DCT<sup>60</sup>.

Differential diagnostic uncertainty can arise in older children or adults with later onset or a milder phenotype. The thiazide test is based on the fact that in GS the sodium-chloride cotransporter NCC, which is the target of thiazide diuretics, is dysfunctional. Thus, patients with GS tend to show a reduced response to thiazide

administration. A cut-off for change in fractional chloride excretion of 2.3% had a sensitivity of 93% and specificity of 100% in separating adult as well as childhood-adolescent GS patients with mutations in *SLC12A3* (encoding NCC) from BS patients with *SLC12A1* and *CLCNKB* mutations<sup>60,61</sup>. All BS3 patients ended up above this threshold and, while clinical characteristics of this subgroup are not described, the variation in calcium excretion in the BS group suggested that this group also included hypocalciuric patients. Nozu *et al* however performed thiazide as well as furosemide testing in a limited number of genetically proven BS and GS patients<sup>62</sup>. Only the BS1 patients showed a clearly reduced response to furosemide, which targets the sodium-potassium-chloride cotransporter that is mutated in these patients. In this study, both GS and BS3 patients with a hypocalciuric phenotype demonstrated reduced responses to thiazides. A blunted thiazide test was also reported in hypomagnesemic patients with *HNF1B* and *FXYD2* mutations who displayed a distal tubular phenotype similar to GS<sup>63,64</sup>. Furthermore, results of both furosemide and thiazide testing depend on age and kidney function<sup>64</sup>. Thus, tubular function tests cannot be used to definitively confirm or exclude a diagnosis of BS. We therefore advise against routine tubular function testing in patients with hypokalemic alkalosis, in line with the KDIGO consensus statement on GS<sup>65</sup>. However, in individual challenging cases or for research purposes, in adult patients, a thiazide test, together with deep genetic testing, could be an option in highly specialized (tertiary) medical centers in order to refine the patient's phenotype.

## V. THERAPY

### *Prenatal therapy*

Pregnancies complicated by polyhydramnios are at risk of adverse pregnancy outcomes, including perinatal mortality. The risk depends on the severity and etiology of polyhydramnios<sup>66</sup> and is related in part to preterm delivery and complications of premature birth<sup>67,68</sup>. Therefore, treatments aimed at reducing amniotic fluid by removal or by inhibiting fetal polyuria appear logical. Serial amniocenteses are commonly used in the intent of prolonging pregnancies, but the benefits of this strategy have not been evaluated in prospective studies. In large case series, the complication rates including fetal demise and prematurity have been reported in 1.5-3.0% of procedures<sup>69,70</sup>.

As an alternative strategy, maternal treatment with NSAIDs might be considered. Apparent efficacy of this treatment has been reported in individual cases of polyhydramnios secondary to different causes and in idiopathic polyhydramnios<sup>71</sup>. Maternal side effects are generally mild and mainly restricted to gastrointestinal symptoms. However, the treatment carries significant risks for the fetus, especially of fetal ductus arteriosus constriction, which increases with advancing gestational age. The risk is close to 50% at 32 weeks of gestation and constriction usually resolves within 24 hours after treatment discontinuation<sup>71</sup>. Therefore, close monitoring by fetal echocardiography is mandatory in all cases of maternal NSAID therapy. Other reported complications include neonatal intestinal perforation and necrotizing enterocolitis, with an incidence of 17% in premature neonates born within one week of indomethacin exposure, as opposed to 6% in matched controls<sup>71</sup>.

To date, only few cases of BS with positive outcome after serial amniocentesis and/or prenatal indomethacin therapy have been

reported; the age at delivery was 34-36 weeks and postnatal outcome was favorable<sup>72-75</sup>. A substantial publication bias towards favorable outcomes, however, cannot be excluded.

Given the above-mentioned risks and lack of prospective studies, a formal recommendation cannot be made. If prenatal intervention is considered for polyhydramnios related to BS, a multidisciplinary perinatal team is mandatory, including a maternal-fetal medicine specialist, a neonatologist, a pediatric cardiologist (in case of NSAID therapy) and a pediatric nephrologist.

### ***Postnatal therapy***

#### **Salt supplementation**

BS is primarily a salt wasting disorder. While plasma sodium concentrations are typically normal, this reflects the concomitant volume loss. Micropuncture data suggest that under physiologic conditions about 5-15% of filtered sodium is reabsorbed in TAL, which in an adult would represent approximately 900-2700 mmol per day (reviewed in<sup>76</sup>). With impaired GFR, this amount will obviously be lower, yet, nevertheless, with salt reabsorption knocked-out in TAL in BS, the salt loss will lead to contraction of the extracellular volume and compensatory upregulation of sodium reabsorption in other tubular segments. Indeed, it is the increased sodium reabsorption in the principal cells of the collecting duct that generates the characteristic electrolyte profile of BS, the hypokalemic, hypochloremic metabolic alkalosis<sup>1</sup>. Thus, supplementation with sodium-chloride constitutes a physiological treatment that can support extracellular volume and improve electrolyte abnormalities and has been recommended at least 5-10 mmol/kg/d<sup>77</sup>. Beyond infancy, once patients can self-determine their dietary intake, some of this supplementation may be provided by the salt craving and high spontaneous salt intake that is typical for BS.

Some patients with BS1 and 2 have a secondary form of nephrogenic diabetes insipidus (NDI)<sup>78,79</sup>. These patients present a therapeutic dilemma as salt supplementation increases the solute load and thus will worsen polyuria and risk hypernatremic dehydration. We recommend against salt supplementation in patients with hypernatremic dehydration and a concomitant urine osmolality lower than plasma or a history thereof.

#### **Potassium supplementation**

If potassium is supplemented, potassium chloride should be used, since chloride is the main anion lost to the urine and patients are alkalotic<sup>43</sup>. Potassium salts (e.g. citrate) should not be used because they potentially worsen the metabolic disturbance by aggravating the alkalosis. This recommendation has also been made for the related disorder GS<sup>65</sup>.

Hypokalemia is a key feature of BS and can be associated with severe complications, including paralysis, rhabdomyolysis, cardiac rhythm abnormalities and sudden death<sup>80-82</sup>. Therefore, potassium supplementation is commonly prescribed in BS. Yet, due to the massively upregulated sodium reabsorption in the collecting duct, renal potassium losses are enormous and the amount of potassium excreted may exceed the amount filtered<sup>43</sup>. While plasma potassium levels increase with supplementation, this results in an increased filtered load and consequently increased urinary losses. Supplemented potassium is thus typically lost in the urine within a few hours<sup>1</sup>. Hence, plasma potassium levels depend heavily on timing of the last dose. Potassium supplements should not be taken

on an empty stomach, otherwise this can generate ulcers. The following recommendation, made for GS, equally applies to BS: KCl supplements can be administered in water or in a slow-release formulation according to each patient's preference. The dose will be titrated according to an individual balance (side-effects vs. symptoms), knowing that the maintenance dose may be high. Potassium-rich aliments should be advised, with the caution that some of them contain high carbohydrate and calories. The target level for plasma potassium is not exactly known, but a reasonable target level may be 3.0 mmol/l. Also in GS, a level of 3.0 mmol/l has been suggested with the explicit acknowledgement that this may not be achievable in some patients<sup>65</sup>. Supplementation with large doses may result in serious side effects including gastric ulcers, vomiting or diarrhoea with worsening biochemistries. A balance between improvement in blood values and side effects should be established on an individual basis. Realistic target values may be lower for some patients and may also change with time.

#### **- Magnesium supplementation**

If magnesium needs to be supplemented (mainly in patients with BS3), oral administration of magnesium salts should be preferred. In this context, it is important to note that hypomagnesemia may aggravate hypokalemia and thus may render it refractory to potassium. Organic salts (e.g. aspartate, citrate, lactate) have a higher bioavailability than magnesium oxide or hydroxide<sup>83</sup>. Exact target levels for magnesium in BS are unknown but a level > 0.6 mmol/l appears reasonable.

We recommend spreading out salt and electrolyte supplements throughout the day, as much as possible.

As urinary salt (Na, Cl, K, +/- Mg) losses are continuous, ideal supplementation would be as close to continuous as possible, to maintain stable steady state levels. Infrequent large doses of supplementation will cause changes in plasma volume or electrolyte levels only for a short period of time and due to the increased filtered load will augment urinary losses. Measured blood levels may vary substantially, depending on timing of the sample in relation to the last dose. There are no clinical studies investigating this, but arguably, large variations in plasma levels may be more detrimental than subnormal but steady levels. We therefore recommend dividing supplementation into as many doses as tolerable for the patient. In infants receiving continuous tube feeds, supplements should be added into the feed. Older patients may prefer to mix the daily dose in a bottle of water, from which they can drink throughout the day.

#### **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

Chloride reabsorption in the macula densa is a key signal in tubuloglomerular feedback (TGF)<sup>84,85</sup>. Decreased chloride reabsorption leads to induction of cyclooxygenase-2 (COX2), with enhanced prostaglandin production and consequent renin release from juxtaglomerular cells<sup>86</sup>. Since the macula densa is part of the TAL and since sodium-chloride reabsorption is impaired in BS, TGF is impaired in patients with BS with upregulation of COX2, explaining the dramatically elevated levels of prostaglandins and renin in BS, as well as the hypertrophy of the juxtaglomerular apparatus, that was part of the initial description of the syndrome by Bartter<sup>9,10</sup>. Based on the underlying pathophysiology it therefore makes sense to pharmacologically suppress COX2 activity and multiple clinical observational studies have shown benefit, in the form of improved growth and electrolyte profile<sup>87-90</sup>. The use of



selective COX2 inhibition has also been reported in BS <sup>9,91-93</sup>. Commonly used NSAIDs in BS are indomethacin (1-4 mg/kg/d divided in 3-4 doses), Ibuprofen (15-30 mg/kg daily in 3 divided doses) and Celecoxib (2-10 mg/kg/d in 2 divided doses). However, the recognition that use of the selective COX2 inhibitor rofecoxib in adults with chronic pain was associated with increased cardiovascular risks has left to the withdrawal of most medications in this class, except for celecoxib <sup>94</sup>. It is unclear, to what degree these cardiovascular risks apply to patients with BS, but interestingly, higher blood pressures, albeit still in the normal range, were noted in patients with BS when treated with rofecoxib compared to indomethacin <sup>95</sup>. There is currently not sufficient evidence to make a recommendation for the use of a specific NSAID in BS and the risks of gastrointestinal and cardiovascular side effects need to be considered individually. Especially if used in the first few weeks or months of life in premature neonates, the risk of necrotising enterocolitis should be carefully considered. It is also important to note that rehydration should be achieved before initiating NSAID therapy because the potential nephrotoxicity depends on the volume status.

The efficacy of NSAIDs in tubulopathies such as BS is sometimes erroneously ascribed to a reduction in GFR, with consequently reduced urinary salt losses (“chemical nephrectomy”). In clinical experience, however, commencement of NSAIDs in BS typically results in clinical improvement, including a stable or even increased GFR, likely reflecting the enhanced volume status <sup>76</sup>. Chronic use of NSAIDs for pain is strongly associated with chronic kidney disease (“analgesic nephropathy”) <sup>96</sup>. Whether this increased risk also applies to patients with BS has been disputed <sup>97,98</sup>. While CKD is a common complication of BS, the aetiology of this is likely manifold, including prematurity and recurrent episodes of dehydration, so that the specific role of NSAIDs is difficult to determine. Arguably, the elevated levels of prostaglandins and renin in BS, which are the indication for NSAIDs, may protect against at least some of the toxicity observed in patients with intact TGF. Indeed, it has been speculated that the persistent elevation of prostaglandins, renin and aldosterone with consequent glomerular hyperfiltration may cause glomerular damage and that life-long treatment with prostaglandin synthesis inhibitors may therefore actually protect, rather than impair long-term kidney function <sup>9,35,99</sup>. Nevertheless, there are reports of “tolerance” to NSAIDs over time, as well as discontinuation of NSAIDs at school age due to a perceived lack of efficacy <sup>43,89</sup>. It is unclear, whether this is related to (insufficient) dosing or a change in the pathophysiology and whether at some point, the risks of NSAIDs may outweigh the benefits. In the absence of good clinical evidence, chronic use of NSAIDs should be considered carefully in each individual patient and tapering down or cessation may be indicated in stable patients.

#### Gastric acid inhibitors

Indomethacin and ibuprofen are non-selective inhibitors of COX enzymes, affecting both COX1 and COX2 isoforms. In contrast, celecoxib primarily inhibits COX2. COX1 is expressed in multiple tissues and inhibition is associated with potentially serious and well recognised side effects, such as gastric ulcers, necrotising enterocolitis and intestinal perforation, which have been recurrently reported also in patients with BS receiving NSAIDs <sup>43,89,100,101</sup>. Thus, if non-selective COX inhibitors are prescribed this should be accompanied by gastric acid suppression. If proton pump

inhibitors (PPI) are used, there is a small risk of PPI associated hypomagnesaemia that could compound renal magnesium wasting. Conversion to H2-blockers or other antacids is recommended in those instances.

#### Supportive treatment

Growth failure is a common complication of BS and often part of the initial presentation. As with other chronic renal conditions, dietetic support is important to maximise caloric intake and facilitate optimal growth. Especially in infants and young children, tube feeding may need to be considered. A feeding tube will not only help to achieve adequate caloric intake, but also the administration of salt supplements.

#### K-sparing diuretics, ACEi and ARBs, thiazides

The hypokalemic alkalosis of BS is generated in the collecting duct, mediated by aldosterone (reviewed in <sup>1</sup>). Consequently, K-sparing diuretics, as well as drugs suppressing the renin-angiotensin system, such as angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) can help ameliorate the electrolyte abnormalities in BS and their use has been recurrently reported <sup>37,43,102-104</sup>. It is important to remember, however, that BS is primarily a salt wasting disorder and that the enhanced sodium reabsorption in the collecting duct is one of the key mechanisms to compensate for the lack of salt reabsorption in TAL. Consequently, drugs that inhibit distal sodium reabsorption, while improving abnormalities in plasma electrolyte concentrations, worsen the salt wasting and risk critical hypovolemia. Arguably, some of the sudden deaths reported in BS may have been caused by hypovolemia, rather than hypokalemia <sup>1</sup>. We therefore do not recommend the routine use of these drugs. Instead, they should be considered carefully in individual cases and may be indicated in those who have severe symptoms from the electrolyte abnormalities, such as recurrent paralysis, cardiac rhythm or respiratory disturbances, despite maximisation of routine treatment with NSAIDs and salt supplements <sup>105</sup>.

Thiazides are occasionally used in an attempt to reduce calcium excretion, also in BS. There are no data on efficacy. Considering the pathophysiology of BS, compensatory salt reabsorption in the DCT is critical for maintenance of volume homeostasis. This is reflected also by the massive hypertrophy of the DCT in animal models of BS <sup>106</sup>. In the absence of informative clinical data, the use of thiazides in BS should be discouraged.

#### Growth Hormone

Growth failure with growth hormone (GH) deficiency in BS has been reported recurrently <sup>40,43,107-109</sup>. Whether this is an intrinsic part of the disorder or a secondary complication of the altered acid-base and/or electrolyte homeostasis is unclear, but two lines of evidence suggest the latter:

- most reports of GH deficiency concerned patients with BS3, who have the most severe abnormalities in acid-base and electrolyte homeostasis (see above);
- severe alkalosis will affect proton binding to proteins, including enzymes and by that may affect charge and consequently folding and function of these proteins. A dramatic improvement in multiple physiological pathways with correction of alkalosis has been reported <sup>105</sup>.



In addition, elevated systemic prostaglandins may contribute to growth failure. In one report, a patient with BS3 and GH deficiency failed to respond to rhGH supplementation until treatment with a COX inhibitor was commenced<sup>43</sup>. Thus, before commencement of rhGH, optimization of metabolic control should be attempted.

## VI. FOLLOW-UP

We suggest that patients should be followed at regular intervals by physicians with a special expertise in renal tubular disorders. Clinical and biochemical features and complications vary widely depending on the underlying molecular defect and between individual patients. Therefore, treatment and follow-up should be tailored to the patient on the basis of clinical manifestation, medical history, stage of development, molecular defect and the clinician's expert judgement. The experts should be in close contact with the patient's local health care provider (general practitioners and/or paediatricians). In addition, according to age and/or genotype, other professions might be involved such as dieticians, social workers, psychologists, endocrinologists and otolaryngologists (BS4).

At each follow-up visit, the following clinical features should be addressed: hydration status, degree of polyuria, and muscular weakness. In children, there is also special emphasis on growth (weight, height, height velocity) and pubertal development. In addition, adverse effects of NSAIDs should be sought. In case of intercurrent illness, it has to be kept in mind that NSAIDs might prevent fever and may thus mask the severity of infectious diseases. Regular biochemical work-up includes acid base status, serum electrolytes (including bicarbonate, chloride and magnesium), renal function (creatinine or cystatin C), PTH, and urinary calcium excretion. Renin and aldosterone levels may be helpful in assessing the adequacy of NSAID treatment. Urine osmolality can help identify those patients with secondary NDI. Renal ultrasound should be performed every 12-24 months for monitoring of nephrocalcinosis/kidney stones. Moreover, it might prove helpful for the assessment of bladder dysfunction and secondary obstructive uropathy as a consequence of polyuria.

During follow-up, the routine assessment of quality of life (QoL) using age-specific standardized questionnaires would be highly desirable. First small case series in patients with salt losing tubulopathies showed that QoL scores are directly influenced by different biochemical parameters such as aldosterone or potassium and thus may help to define better therapeutic targets in the future<sup>110</sup>.

### Long term outcomes and complications

Published data on long term outcomes and prognosis in BS are sparse. Whereas nephrocalcinosis and hypercalciuria are present in the majority of patients (except BS3 patients with a Gitelman-like phenotype), the prevalence of (symptomatic) urolithiasis in BS appears relatively low<sup>37</sup>, but extensive data are lacking<sup>111</sup>. Nephrotic range proteinuria has also been reported in BS patients<sup>40,43,112</sup>. When renal biopsies are performed, they often show diffuse glomerular and tubulointerstitial lesions with enlarged glomeruli and FSGS<sup>37</sup>. Some, but not all showed juxtaglomerular apparatus hypertrophy. Recently, Seys et al suggested that patients with BS1 and BS4 had more severe eGFR decrease and showed

more CKD stage 3-5 than BS2 and BS3<sup>37,97</sup>. Next to the molecular defect itself (especially in BS4<sup>97</sup>, other risk factors potentially contributing to chronic kidney injury could be premature birth/low birth weight, nephrocalcinosis, chronic dehydration state and progressive proteinuria related to hyperfiltration because of RAS activation, treatment with NSAIDs (while contradictory data have been published; also see above) and hypokalemia. True hypokalemic nephropathy has been suggested to occur in animal studies<sup>113,114</sup>, but whether it is a real entity in humans is controversial<sup>115</sup>. In both GS and BS patients, there seems to be no correlation between serum potassium levels and eGFR<sup>37,115</sup>. Some patients progress to end-stage kidney disease (ESKD) and require dialysis or kidney transplantation, but exact data are lacking. To date, only a small number of kidney transplantations at an age between 11 and 27 years (cadaveric and living-related) has been reported in the literature<sup>37,116-122</sup>. Interestingly, the underlying molecular defects in most of the cases were in *CLCNKB*, suggesting that chronic hyperfiltration and/or the more severe electrolyte abnormalities in BS3 are the most important risk factors for ESKD. Pre-emptive nephrectomy and kidney transplantation before reaching ESKD has been reported, but is not routinely performed nor recommended<sup>123</sup>. As expected, in all cases, the electrolyte abnormalities and polyuria were corrected and recurrent disease was not observed.

### Cardiac work-up/anaesthesia/sports

Hypokalemia with or without additional magnesium depletion prolongs the duration of the action potential in cardiomyocytes, resulting in prolonged QT interval which could lead to an increased risk for ventricular arrhythmias. Isolated reports on cardiac arrhythmias, long QT and sudden death have been reported in BS patients<sup>80,124,125</sup>, therefore an electrocardiogram (ECG) should be performed at rest to assess rhythm and QT duration. A further cardiology workup, as previously recommended for GS<sup>65</sup>, is indicated when patients complain of palpitations or syncope (e.g., Holter, stress ECG), or if the ECG abnormalities persist despite attempted improvement of the biochemical abnormalities<sup>126</sup>. Drugs slowing sinus rhythm or influencing the QT interval such as negative chronotropic drugs or drugs potentially inducing or exacerbating hypomagnesemia such as proton-pump inhibitors, macrolides, fluorquinolones, gentamicin, antiviral drugs, should be avoided.

Caution should be taken when patients with Bartter's syndrome undergo anaesthesia. Hypokalemia and hypomagnesemia can potentiate the effects of local and general anesthetic agents such as neuromuscular blockade during general anaesthesia and adrenalin use in regional blockade. However, there is no definitive evidence to suggest exact preoperative levels of potassium that is safe. In the general population, guidelines suggest aiming for potassium levels above 3.0 mmol/l (and magnesium above 0.5 mmol/l)<sup>127</sup>. In BS, there is no evidence suggesting that participation in sports is deleterious. In any case, volume depletion should be prevented and additional salt or electrolytes or both may help. However, strenuous exercise or competition practice should be avoided in particular in cases of a history of cardiac manifestations or prolonged QT when a cardiology workup is advised.

### **Pregnancy considerations**

Pregnancy is associated with a stimulation of the renin-angiotensin-aldosterone system, which potentially aggravates renal potassium wasting<sup>128</sup>. This effect is, at least in part, counterbalanced by marked hemodynamic changes (systemic vasodilatation) and increases in plasma progesterone levels<sup>129</sup>. However, during normal pregnancy, serum potassium levels decrease by 0.2 – 0.5 mmol/l around midgestation<sup>13,130</sup>. Thus, in pregnant women with BS, the timely institution of a joint management plan involving nephrology and obstetrics as well as appropriate adaptations in therapy is mandatory. In patients with BS, the occurrence of hyperemesis gravidarum may be particularly dangerous because of the subsequent electrolyte disturbances that may necessitate early parenteral fluid and electrolyte supplementation. During pregnancy, the target level for plasma potassium is unknown, but generally speaking, a level of 3.0 mmol/l has been suggested with the explicit acknowledgement that this may not be achievable in some patients<sup>65</sup>. Pregnant women with BS should be informed about increased requirements of electrolyte supplements, that RAS blockers are contraindicated, and that NSAIDs are discouraged during pregnancy. Monitoring of plasma electrolyte levels is advised during labour. Therefore, in hospital childbirth might be considered to reduce risks of maternal complications. The overall outcome for women with BS and their infants described to date is favourable<sup>129,131-134</sup>. This includes cases where the diagnosis of BS was unknown before pregnancy<sup>129,133,135</sup>. After delivery, the treatment of the mother may return to baseline supplementation.

### **VII. PATIENT EDUCATION**

Disease specific education for patients suffering from BS and their families is highly important for patient empowerment. Information can be provided through various channels, including age appropriate personal education, information leaflets, web-based information with special pages directly addressing patients and parents, patient-led forums and patient and family group support events (table 5). Furthermore, it is vital that patients know what to do in case of emergency.

Medical identity bracelets should be considered to alert acute care doctors to the underlying diagnosis in case of sudden deteriorations. A medical report that lists disease specific information and prescribed medications should always be carried by patients while travelling. Patients should be allowed to carry their medications on board an aircraft.

“Sick day rules” may be helpful in case of intercurrent illness (table 6).

BS itself and comorbidities resulting from extreme prematurity in a subset of BS patients can compromise school performance (e.g. difficulty to concentrate, learning disabilities, school absence). Depending on the country, various measures to support these children may be available and should be utilized.

Work performance can be limited in older patients. Occupational therapists may in some instances (e.g. in large companies) be able to assist patients in finding support for their individual situation. Consideration for extra rest time, reduced workload or the option to work from home may allow patients to still participate in work life if, for example, muscle weakness or fatigue prevent patients from working full time.

Patients are often hesitant to disclose their condition to employers because they are afraid to lose their job. However, patients should be encouraged to share information about the disease, ideally by providing educational material about BS.

### **VIII. CONCLUSION AND PERSPECTIVES**

The identification of genes involved in BS with the consequent insights into the molecular pathophysiology is relatively recent. Therefore, long-term follow-up data from genetically defined cohorts are limited. With time, as more such data become available, our knowledge of the natural history, treatment response and long-term complications and quality of life will improve, and thus directly influence patient management. We thus anticipate that as more data become available, the recommendations made here will need to be updated and revised.

## ACKNOWLEDGMENT

This consensus document has been supported by the European Reference Network for Rare Kidney Diseases (ERKNet), which is partly co-funded by the European Union within the framework of the Third Health Programme 'ERN-2016-Framework Partnership Agreement 2017-2021'. The funder had no influence on the content of the consensus. The authors also thank Tanja Wlodkowski, Heidelberg for her continuous support concerning the literature search and the panel voting procedures.

## COMPETING INTERESTS

The authors declare no competing interests.

## APPENDIX

- Figures and Tables
- Box 1 Recommendations for diagnosis of Bartter syndrome
- Box 2 Recommendations for therapy of Bartter syndrome
- Box 3 Recommendations for follow-up of patients with Bartter syndrome

## REFERENCES

- 1 Kleta, R. & Bockenhauer, D. Salt-Losing Tubulopathies in Children: What's New, What's Controversial? *J Am Soc Nephrol* **29**, 727-739 (2018).
- 2 Colussi, G. Bartter syndrome, <[https://www.orpha.net/consor/cgi-bin/Disease\\_Search.php?lng=EN&data\\_id=259](https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=259)> (2014).
- 3 Ji, W. *et al.* Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* **40**, 592-599 (2008).
- 4 Gill, J. R., Jr. & Bartter, F. C. Evidence for a prostaglandin-independent defect in chloride reabsorption in the loop of Henle as a proximal cause of Bartter's syndrome. *Am J Med* **65**, 766-772 (1978).
- 5 Bettinelli, A. *et al.* Use of calcium excretion values to distinguish two forms of primary renal tubular hypokalemic alkalosis: Bartter and Gitelman syndromes. *J Pediatr* **120**, 38-43 (1992).
- 6 Schnermann, J. Homer W. Smith Award lecture. The juxtaglomerular apparatus: from anatomical peculiarity to physiological relevance. *J Am Soc Nephrol* **14**, 1681-1694 (2003).
- 7 Bartter, F. C. *et al.* Prostaglandins are overproduced by the kidneys and mediate hyperreninemia in Bartter's syndrome. *Trans Assoc Am Physicians* **89**, 77-91 (1976).
- 8 Seyberth, H. W. *et al.* Congenital hypokalemia with hypercalciuria in preterm infants: a hyperprostaglandinuric tubular syndrome different from Bartter syndrome. *J Pediatr* **107**, 694-701 (1985).
- 9 Reinalter, S. C. *et al.* Role of cyclooxygenase-2 in hyperprostaglandin E syndrome/antenatal Bartter syndrome. *Kidney Int* **62**, 253-260 (2002).
- 10 Bartter, F. C., Pronove, P., Gill, J. R., Jr. & Maccardle, R. C. Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis. A new syndrome. *Am J Med* **33**, 811-828 (1962).
- 11 Fanconi, A., Schachenmann, G., Nussli, R. & Prader, A. Chronic hypokalaemia with growth retardation, normotensive hyperrenin-hyperaldosteronism ("Bartter's syndrome"), and hypercalciuria. Report of two cases with emphasis on natural history and on catch-up growth during treatment. *Helv Paediatr Acta* **26**, 144-163 (1971).
- 12 Ohlsson, A., Sieck, U., Cumming, W., Akhtar, M. & Serenius, F. A variant of Bartter's syndrome. Bartter's syndrome associated with hydramnios, prematurity, hypercalciuria and nephrocalcinosis. *Acta Paediatr Scand* **73**, 868-874 (1984).
- 13 Stein, J. H. The pathogenetic spectrum of Bartter's syndrome. *Kidney Int* **28**, 85-93 (1985).
- 14 Simon, D. B. *et al.* Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. *Nat Genet* **13**, 183-188 (1996).
- 15 Simon, D. B. *et al.* Genetic heterogeneity of Bartter's syndrome revealed by mutations in the K<sup>+</sup> channel, ROMK. *Nat Genet* **14**, 152-156 (1996).
- 16 Simon, D. B. *et al.* Mutations in the chloride channel gene, CLCNKB, cause Bartter's syndrome type III. *Nat Genet* **17**, 171-178 (1997).
- 17 Birkenhager, R. *et al.* Mutation of BSND causes Bartter syndrome with sensorineural deafness and kidney failure. *Nat Genet* **29**, 310-314 (2001).
- 18 Estevez, R. *et al.* Barttin is a Cl<sup>-</sup> channel beta-subunit crucial for renal Cl<sup>-</sup> reabsorption and inner ear K<sup>+</sup> secretion. *Nature* **414**, 558-561 (2001).
- 19 Schlingmann, K. P. *et al.* Salt wasting and deafness resulting from mutations in two chloride channels. *N Engl J Med* **350**, 1314-1319 (2004).
- 20 Garcia-Nieto, V. *et al.* Mutation G47R in the BSND gene causes Bartter syndrome with deafness in two Spanish families. *Pediatr Nephrol* **21**, 643-648 (2006).
- 21 Brum, S., Rueff, J., Santos, J. R. & Calado, J. Unusual adult-onset manifestation of an attenuated Bartter's syndrome type IV renal phenotype caused by a mutation in BSND. *Nephrol Dial Transplant* **22**, 288-289 (2007).
- 22 Riazuddin, S. *et al.* Molecular basis of DFNB73: mutations of BSND can cause nonsyndromic deafness or Bartter syndrome. *Am J Hum Genet* **85**, 273-280 (2009).
- 23 Laghmani, K. *et al.* Polyhydramnios, Transient Antenatal Bartter's Syndrome, and MAGED2 Mutations. *N Engl J Med* **374**, 1853-1863 (2016).
- 24 Vargas-Poussou, R. *et al.* Functional characterization of a calcium-sensing receptor mutation in severe autosomal dominant hypocalcemia with a Bartter-like syndrome. *J Am Soc Nephrol* **13**, 2259-2266 (2002).
- 25 Jeck, N. *et al.* Salt handling in the distal nephron: lessons learned from inherited human disorders. *Am J Physiol Regul Integr Comp Physiol* **288**, R782-795 (2005).
- 26 American Academy of Pediatrics Steering Committee on Quality, I. & Management. Classifying recommendations for clinical practice guidelines. *Pediatrics* **114**, 874-877 (2004).
- 27 Flynn, J. T. *et al.* Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics* **140** (2017).
- 28 Ashton, E. J. *et al.* Simultaneous sequencing of 37 genes identified causative mutations in the majority of children with renal tubulopathies. *Kidney Int* **93**, 961-967 (2018).
- 29 Massa, G. *et al.* Electrolyte composition of the amniotic fluid in Bartter syndrome. *Eur J Obstet Gynecol Reprod Biol* **24**, 335-340 (1987).
- 30 Shalev, H., Ohaly, M., Meizner, I. & Carmi, R. Prenatal diagnosis of Bartter syndrome. *Prenat Diagn* **14**, 996-998 (1994).
- 31 Rachid, M. L. *et al.* Prenatal diagnosis of Bartter syndrome: amniotic fluid aldosterone. *Prenat Diagn* **36**, 88-91 (2016).
- 32 Garnier, A. *et al.* Bartter syndrome prenatal diagnosis based on amniotic fluid biochemical analysis. *Pediatr Res* **67**, 300-303 (2010).
- 33 Allaf, B. *et al.* Amniotic fluid biochemistry in isolated polyhydramnios: a series of 464 cases. *Prenat Diagn* **35**, 1331-1335 (2015).
- 34 Brochard, K. *et al.* Phenotype-genotype correlation in antenatal and neonatal variants of Bartter syndrome. *Nephrol Dial Transplant* **24**, 1455-1464 (2009).
- 35 Komhoff, M. & Laghmani, K. Pathophysiology of antenatal Bartter's syndrome. *Curr Opin Nephrol Hypertens* **26**, 419-425 (2017).
- 36 Legrand, A. *et al.* Prevalence of Novel MAGED2 Mutations in Antenatal Bartter Syndrome. *Clin J Am Soc Nephrol* **13**, 242-250 (2018).
- 37 Seys, E. *et al.* Clinical and Genetic Spectrum of Bartter Syndrome Type 3. *J Am Soc Nephrol* **28**, 2540-2552 (2017).

- 38 Konrad, M. *et al.* Mutations in the chloride channel gene CLCNKB as a cause of classic Bartter syndrome. *J Am Soc Nephrol* **11**, 1449-1459 (2000).
- 39 Peters, M. *et al.* Clinical presentation of genetically defined patients with hypokalemic salt-losing tubulopathies. *Am J Med* **112**, 183-190 (2002).
- 40 Bettinelli, A. *et al.* Patients with biallelic mutations in the chloride channel gene CLCNKB: long-term management and outcome. *Am J Kidney Dis* **49**, 91-98 (2007).
- 41 Lee, B. H. *et al.* Genetic basis of Bartter syndrome in Korea. *Nephrol Dial Transplant* **27**, 1516-1521 (2012).
- 42 Garcia Castano, A. *et al.* Poor phenotype-genotype association in a large series of patients with Type III Bartter syndrome. *PLoS One* **12**, e0173581 (2017).
- 43 Walsh, P. R. *et al.* Clinical and diagnostic features of Bartter and Gitelman syndromes. *Clin Kidney J* **11**, 302-309 (2018).
- 44 Garcia Castano, A. *et al.* Genetics of type III Bartter syndrome in Spain, proposed diagnostic algorithm. *PLoS One* **8**, e74673 (2013).
- 45 Finer, G. *et al.* Transient neonatal hyperkalemia in the antenatal (ROMK defective) Bartter syndrome. *J Pediatr* **142**, 318-323 (2003).
- 46 Jeck, N. *et al.* Mutations in the chloride channel gene, CLCNKB, leading to a mixed Bartter-Gitelman phenotype. *Pediatr Res* **48**, 754-758 (2000).
- 47 Zelikovic, I. *et al.* A novel mutation in the chloride channel gene, CLCNKB, as a cause of Gitelman and Bartter syndromes. *Kidney Int* **63**, 24-32 (2003).
- 48 Hureau, M. *et al.* High-throughput sequencing contributes to the diagnosis of tubulopathies and familial hypercalcemia hypocalciuria in adults. *Kidney Int* **96**, 1408-1416 (2019).
- 49 Feldmann, D., Alessandri, J. L. & Deschenes, G. Large deletion of the 5' end of the ROMK1 gene causes antenatal Bartter syndrome. *J Am Soc Nephrol* **9**, 2357-2359 (1998).
- 50 Lazebnik, N. & Many, A. The severity of polyhydramnios, estimated fetal weight and preterm delivery are independent risk factors for the presence of congenital malformations. *Gynecol Obstet Invest* **48**, 28-32 (1999).
- 51 Dashe, J. S., McIntire, D. D., Ramus, R. M., Santos-Ramos, R. & Twickler, D. M. Hydramnios: anomaly prevalence and sonographic detection. *Obstet Gynecol* **100**, 134-139 (2002).
- 52 Wedenoja, S., Hoglund, P. & Holmberg, C. Review article: the clinical management of congenital chloride diarrhoea. *Aliment Pharmacol Ther* **31**, 477-485 (2010).
- 53 Adalat, S. *et al.* HNF1B Mutations Are Associated With a Gitelman-like Tubulopathy That Develops During Childhood. *Kidney Int Rep* **4**, 1304-1311 (2019).
- 54 Bongers, E. *et al.* A Novel Hypokalemic-Alkalotic Salt-Losing Tubulopathy in Patients with CLDN10 Mutations. *J Am Soc Nephrol* **28**, 3118-3128 (2017).
- 55 Hadj-Rabia, S. *et al.* Multiplex epithelium dysfunction due to CLDN10 mutation: the HELIX syndrome. *Genet Med* **20**, 190-201 (2018).
- 56 Bockenhauer, D. *et al.* Epilepsy, ataxia, sensorineural deafness, tubulopathy, and KCNJ10 mutations. *N Engl J Med* **360**, 1960-1970 (2009).
- 57 Cooper, M. & Stewart, P. M. The syndrome of apparent mineralocorticoid excess. *QJM* **91**, 453-455 (1998).
- 58 Palmer, B. F. A physiologic-based approach to the evaluation of a patient with hypokalemia. *Am J Kidney Dis* **56**, 1184-1190 (2010).
- 59 Wu, K. L. *et al.* Identification of the Causes for Chronic Hypokalemia: Importance of Urinary Sodium and Chloride Excretion. *Am J Med* **130**, 846-855 (2017).
- 60 Colussi, G. *et al.* A thiazide test for the diagnosis of renal tubular hypokalemic disorders. *Clin J Am Soc Nephrol* **2**, 454-460 (2007).
- 61 Peng, X. *et al.* Hydrochlorothiazide Test as a Tool in the Diagnosis of Gitelman Syndrome in Chinese Patients. *Front Endocrinol (Lausanne)* **9**, 559 (2018).
- 62 Nozu, K. *et al.* The pharmacological characteristics of molecular-based inherited salt-losing tubulopathies. *J Clin Endocrinol Metab* **95**, E511-518 (2010).
- 63 Verhave, J. C., Bech, A. P., Wetzels, J. F. & Nijenhuis, T. Hepatocyte Nuclear Factor 1beta-Associated Kidney Disease: More than Renal Cysts and Diabetes. *J Am Soc Nephrol* **27**, 345-353 (2016).
- 64 Bech, A. P., Wetzels, J. F. M. & Nijenhuis, T. Reference values of renal tubular function tests are dependent on age and kidney function. *Physiol Rep* **5**, (2017).
- 65 Blanchard, A. *et al.* Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* **91**, 24-33 (2017).
- 66 Sandlin, A. T., Chauhan, S. P. & Magann, E. F. Clinical relevance of sonographically estimated amniotic fluid volume: polyhydramnios. *J Ultrasound Med* **32**, 851-863 (2013).
- 67 MacKay, D. F., Smith, G. C., Dobbie, R. & Pell, J. P. Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS Med* **7**, e1000289 (2010).
- 68 Marlow, N. Full term; an artificial concept. *Arch Dis Child Fetal Neonatal Ed* **97**, F158-159 (2012).
- 69 Elliott, J. P., Sawyer, A. T., Radin, T. G. & Strong, R. E. Large-volume therapeutic amniocentesis in the treatment of hydramnios. *Obstet Gynecol* **84**, 1025-1027 (1994).
- 70 Leung, W. C., Jouannic, J. M., Hyett, J., Rodeck, C. & Jauniaux, E. Procedure-related complications of rapid amniocentesis in the treatment of polyhydramnios. *Ultrasound Obstet Gynecol* **23**, 154-158 (2004).
- 71 Moise, K. J., Jr. Polyhydramnios. *Clin Obstet Gynecol* **40**, 266-279 (1997).
- 72 Konrad, M., Leonhardt, A., Hensen, P., Seyberth, H. W. & Kockerling, A. Prenatal and postnatal management of hyperprostaglandin E syndrome after genetic diagnosis from amniocytes. *Pediatrics* **103**, 678-683 (1999).
- 73 Tourne, G. *et al.* [Prenatal Bartter's syndrome. Report of two cases]. *J Gynecol Obstet Biol Reprod (Paris)* **32**, 751-754 (2003).
- 74 Dane, B., Dane, C., Aksoy, F., Cetin, A. & Yayla, M. Antenatal Bartter syndrome: analysis of two cases with placental findings. *Fetal Pediatr Pathol* **29**, 121-126 (2010).
- 75 Bhat, Y. R., Vinayaka, G., Vani, R., Prashanth, K. A. & Sreelakshmi, K. Antenatal Bartter syndrome: a rare cause of unexplained severe polyhydramnios. *Ann Trop Paediatr* **31**, 153-157 (2011).
- 76 Bockenhauer, D. *et al.* Antenatal Bartter's syndrome: why is this not a lethal condition? *QJM* **101**, 927-942 (2008).
- 77 Kleta, R. & Bockenhauer, D. Bartter syndromes and other salt-losing tubulopathies. *Nephron Physiol* **104**, p73-80 (2006).
- 78 Bockenhauer, D. *et al.* Secondary nephrogenic diabetes insipidus as a complication of inherited renal diseases. *Nephron Physiol* **116**, p23-29 (2010).
- 79 Bockenhauer, D. & Bichet, D. G. Inherited secondary nephrogenic diabetes insipidus: concentrating on humans. *Am J Physiol Renal Physiol* **304**, F1037-1042 (2013).
- 80 Cortesi, C. *et al.* Severe syncope and sudden death in children with inborn salt-losing hypokalaemic tubulopathies. *Nephrol Dial Transplant* **20**, 1981-1983 (2005).
- 81 Cortesi, C. *et al.* Cardiac arrhythmias and rhabdomyolysis in Bartter-Gitelman patients. *Pediatr Nephrol* **25**, 2005-2008 (2010).
- 82 von Vigier, R. O., Ortisi, M. T., La Manna, A., Bianchetti, M. G. & Bettinelli, A. Hypokalemic rhabdomyolysis in congenital tubular disorders: a case series and a systematic review. *Pediatr Nephrol* **25**, 861-866 (2010).
- 83 Ranade, V. V. & Somberg, J. C. Bioavailability and pharmacokinetics of magnesium after administration of magnesium salts to humans. *Am J Ther* **8**, 345-357 (2001).
- 84 Lorenz, J. N., Weihprecht, H., Schnermann, J., Skott, O. & Briggs, J. P. Renin release from isolated juxtaglomerular apparatus depends on macula densa chloride transport. *Am J Physiol* **260**, F486-493 (1991).
- 85 Peti-Peterdi, J. & Harris, R. C. Macula densa sensing and signaling mechanisms of renin release. *J Am Soc Nephrol* **21**, 1093-1096 (2010).
- 86 Nusing, R. M., Reinalter, S. C., Peters, M., Komhoff, M. & Seyberth, H. W. Pathogenetic role of cyclooxygenase-2 in hyperprostaglandin E syndrome/antenatal Bartter syndrome: therapeutic use of the cyclooxygenase-2 inhibitor nimesulide. *Clin Pharmacol Ther* **70**, 384-390 (2001).
- 87 Littlewood, J. M., Lee, M. R. & Meadow, S. R. Treatment of childhood Bartter's syndrome with indomethacin. *Lancet* **2**, 795 (1976).
- 88 Littlewood, J. M., Lee, M. R. & Meadow, S. R. Treatment of Bartter's syndrome in early childhood with prostaglandin synthetase inhibitors. *Arch Dis Child* **53**, 43-48 (1978).
- 89 Dillon, M. J., Shah, V. & Mitchell, M. D. Bartter's syndrome: 10 cases in childhood. Results of long-term indomethacin therapy. *Q J Med* **48**, 429-446 (1979).

- 90 Seidel, C., Reinalter, S., Seyberth, H. W. & Scharer, K. Pre-pubertal growth in the hyperprostaglandin E syndrome. *Pediatr Nephrol* **9**, 723-728 (1995).
- 91 Kleta, R., Basoglu, C. & Kuwertz-Broking, E. New treatment options for Bartter's syndrome. *N Engl J Med* **343**, 661-662 (2000).
- 92 Komhoff, M. *et al.* Cyclooxygenase-2 expression is associated with the renal macula densa of patients with Bartter-like syndrome. *Kidney Int* **58**, 2420-2424 (2000).
- 93 Haas, N. A. *et al.* Successful management of an extreme example of neonatal hyperprostaglandin-E syndrome (Bartter's syndrome) with the new cyclooxygenase-2 inhibitor rofecoxib. *Pediatr Crit Care Med* **4**, 249-251 (2003).
- 94 Dogne, J. M., Hanson, J., Supuran, C. & Pratico, D. Coxibs and cardiovascular side-effects: from light to shadow. *Curr Pharm Des* **12**, 971-975 (2006).
- 95 Komhoff, M., Klaus, G., Nazarowa, S., Reinalter, S. C. & Seyberth, H. W. Increased systolic blood pressure with rofecoxib in congenital furosemide-like salt loss. *Nephrol Dial Transplant* **21**, 1833-1837 (2006).
- 96 Bennett, W. M. & DeBroe, M. E. Analgesic nephropathy--a preventable renal disease. *N Engl J Med* **320**, 1269-1271 (1989).
- 97 Jeck, N. *et al.* Hypokalemic salt-losing tubulopathy with chronic renal failure and sensorineural deafness. *Pediatrics* **108**, E5 (2001).
- 98 Reinalter, S. C., Grone, H. J., Konrad, M., Seyberth, H. W. & Klaus, G. Evaluation of long-term treatment with indomethacin in hereditary hypokalemic salt-losing tubulopathies. *J Pediatr* **139**, 398-406 (2001).
- 99 Su, I. H. *et al.* Bartter syndrome and focal segmental glomerulosclerosis: a possible link between two diseases. *Pediatr Nephrol* **14**, 970-972 (2000).
- 100 Marlow, N. & Chiswick, M. L. Neonatal Bartter's syndrome, indomethacin and necrotizing enterocolitis. *Acta Paediatr Scand* **71**, 1031-1032 (1982).
- 101 Vane, J. R. & Botting, R. M. Mechanism of action of nonsteroidal anti-inflammatory drugs. *Am J Med* **104**, 2S-8S; discussion 21S-22S (1998).
- 102 Morales, J. M. *et al.* Long-term enalapril therapy in Bartter's syndrome. *Nephron* **48**, 327 (1988).
- 103 Clementsen, P. *et al.* Bartter's syndrome--treatment with potassium, spironolactone and ACE-inhibitor. *J Intern Med* **225**, 107-110 (1989).
- 104 Nascimento, C. L., Garcia, C. L., Schwartsman, B. G. & Vaisbich, M. H. Treatment of Bartter syndrome. Unsolved issue. *J Pediatr (Rio J)* **90**, 512-517 (2014).
- 105 Plumb, L. A. *et al.* Renal apnoea: extreme disturbance of homeostasis in a child with Bartter syndrome type IV. *Lancet* **388**, 631-632 (2016).
- 106 Wagner, C. A. *et al.* Mouse model of type II Bartter's syndrome. II. Altered expression of renal sodium- and water-transporting proteins. *Am J Physiol Renal Physiol* **294**, F1373-1380 (2008).
- 107 Akil, I., Ozen, S., Kandiloglu, A. R. & Ersoy, B. A patient with Bartter syndrome accompanying severe growth hormone deficiency and focal segmental glomerulosclerosis. *Clin Exp Nephrol* **14**, 278-282 (2010).
- 108 Gil-Pena, H., Mejia, N., Alvarez-Garcia, O., Loreda, V. & Santos, F. Longitudinal growth in chronic hypokalemic disorders. *Pediatr Nephrol* **25**, 733-737 (2010).
- 109 Buyukcelik, M., Keskin, M., Kilic, B. D., Kor, Y. & Balat, A. Bartter syndrome and growth hormone deficiency: three cases. *Pediatr Nephrol* **27**, 2145-2148 (2012).
- 110 Eder, M. *et al.* Markers of potassium homeostasis in salt losing tubulopathies- associations with hyperaldosteronism and hypomagnesemia. *BMC nephrology* **21**, 256 (2020).
- 111 Faller, N., Dhayat, N. A. & Fuster, D. G. Nephrolithiasis secondary to inherited defects in the thick ascending loop of henle and connecting tubules. *Urolithiasis* **47**, 43-56 (2019).
- 112 Puricelli, E. *et al.* Long-term follow-up of patients with Bartter syndrome type I and II. *Nephrol Dial Transplant* **25**, 2976-2981 (2010).
- 113 Tsao, T. *et al.* Expression of insulin-like growth factor-I and transforming growth factor-beta in hypokalemic nephropathy in the rat. *Kidney Int* **59**, 96-105 (2001).
- 114 Fervenza, F. C. & Rabkin, R. The role of growth factors and ammonia in the genesis of hypokalemic nephropathy. *J Ren Nutr* **12**, 151-159 (2002).
- 115 Walsh, S. B., Unwin, E., Vargas-Poussou, R., Houillier, P. & Unwin, R. Does hypokalaemia cause nephropathy? An observational study of renal function in patients with Bartter or Gitelman syndrome. *QJM* **104**, 939-944 (2011).
- 116 Blethen, S. L., Van Wyk, J. J., Lorentz, W. B. & Jennette, J. C. Reversal of Bartter's syndrome by renal transplantation in a child with focal, segmental glomerular sclerosis. *Am J Med Sci* **289**, 31-36 (1985).
- 117 Rudin, A. Bartter's syndrome. A review of 28 patients followed for 10 years. *Acta Med Scand* **224**, 165-171 (1988).
- 118 Takahashi, M. *et al.* A first report: living related kidney transplantation on a patient with Bartter's syndrome. *Transplant Proc* **28**, 1588 (1996).
- 119 Kim, J. Y. *et al.* A case of living-related kidney transplantation in Bartter's syndrome. *Yonsei Med J* **41**, 662-665 (2000).
- 120 Ueki, R. *et al.* Perioperative endocrinological findings in a patient with Bartter's syndrome and living-related renal transplantation. *J Anesth* **14**, 105-108 (2000).
- 121 Kitataka, S., Sato, U., Maruyama, K. & Igarashi, T. A compound heterozygous mutation in the BSND gene detected in Bartter syndrome type IV. *Pediatr Nephrol* **21**, 190-193 (2006).
- 122 Lee, S. E. *et al.* Renal transplantation in a patient with Bartter syndrome and glomerulosclerosis. *Korean J Pediatr* **54**, 36-39 (2011).
- 123 Chaudhuri, A., Salvatierra, O., Jr., Alexander, S. R. & Sarwal, M. M. Option of pre-emptive nephrectomy and renal transplantation for Bartter's syndrome. *Pediatr Transplant* **10**, 266-270 (2006).
- 124 Malafrente, C. *et al.* Cardiac arrhythmias due to severe hypokalemia in a patient with classic Bartter disease. *Pediatr Nephrol* **19**, 1413-1415 (2004).
- 125 Scognamiglio, R., Negut, C. & Calo, L. A. Aborted sudden cardiac death in two patients with Bartter's/Gitelman's syndromes. *Clin Nephrol* **67** (2007).
- 126 Scognamiglio, R. *et al.* Myocardial perfusion defects in Bartter and Gitelman syndromes. *Eur J Clin Invest* **38**, 888-895 (2008).
- 127 Gallagher, H., Soar, J. & Tomson, C. New guideline for perioperative management of people with inherited salt-wasting alkaloses. *Br J Anaesth* **116**, 746-749 (2016).
- 128 Carr, B. R. & Gant, N. F. The endocrinology of pregnancy-induced hypertension. *Clin Perinatol* **10**, 737-761 (1983).
- 129 Luqman, A., Kazmi, A. & Wall, B. M. Bartter's syndrome in pregnancy: review of potassium homeostasis in gestation. *Am J Med Sci* **338**, 500-504 (2009).
- 130 Cunningham, D. S., Brodник, R. M., Rayl, D. L., Brown, A. W. & Hansen, K. A. Suboptimal progesterone production in pathologic pregnancies. *J Reprod Med* **38**, 301-305 (1993).
- 131 O'Sullivan, E., Monga, M. & Graves, W. Bartter's syndrome in pregnancy: a case report and review. *Am J Perinatol* **14**, 55-57 (1997).
- 132 Li, I. C. & To, W. W. Bartter's syndrome in pregnancy: a case report and review. *J Obstet Gynaecol Res* **26**, 77-79 (2000).
- 133 Nohira, T. *et al.* Pregnancy complicated with Bartter's syndrome: a case report. *J Obstet Gynaecol Res* **27**, 267-274 (2001).
- 134 Deruelle, P., Dufour, P., Magneant, E., Courouble, N. & Puech, F. Maternal Bartter's syndrome in pregnancy treated by amiloride. *Eur J Obstet Gynecol Reprod Biol* **115**, 106-107 (2004).
- 135 Peregrin-Alvarez, I., Rodriguez-Casares, J., Lucena-Herrera, C., Arribas, F. & Castro, D. Bartter's syndrome and pregnancy. *Eur J Obstet Gynecol Reprod Biol* **121**, 118-119 (2005).

## APPENDIX

Table 2 Main clinical and biochemical characteristics of different types of Bartter syndrome (Data from REFS<sup>35,36</sup>)

	Type 1	Type 2	Type 3	Type 4	Type 5
				4a   4b	
<b>Age at onset</b>	prenatally	prenatally	0-5 years	prenatally	prenatally
<b>Polyhydramnios</b>	severe	severe	absent-mild	severe	very severe
<b>Gestational age at birth (median, IQR)</b>	32 (29-34)	33 (31-35)	37 (36-41)	31 (28-35)	29 (21-37)
<b>Leading symptoms</b>	polyuria hypochloremia alkalosis hypokalemia	polyuria hypochloremia alkalosis transient neonatal hyperkalemia	hypokalemia hypochloremia alkalosis failure to thrive	polyuria hypochloremia alkalosis hypokalemia	polyuria hypochloremia alkalosis hypokalemia
<b>Calcium excretion</b>	high	high	variable	variable	high
<b>Nephrocalcinosis</b>	very frequent	very frequent	rare, mild	rare, mild	rare, mild
<b>Plasma Cl/Na ratio</b>	normal	normal	decreased	decreased	increased
<b>Other findings</b>			mild hypomagnesemia	deafness risk for CKD, ESRD	large for gestational age transient disease

Abbreviations: IQR interquartile range; CKD chronic kidney disease; ESRD end stage renal disease

Table 3 Age-specific reference values (5<sup>th</sup> and 95<sup>th</sup> percentiles) for urinary Ca/Cr ratios in children.

Age (years)	Urinary Ca/Cr	Urinary Ca/Cr
	(mol/mol)	(mg/mg)
<1	0.09-2.2	0.03-0.81
1-2	0.07-1.5	0.02-0.56
2-3	0.06-1.4	0.02-0.50
3-5	0.05-1.1	0.02-0.41
5-7	0.04-0.8	0.01-0.30
7-10	0.04-0.7	0.01-0.25
10-17	0.04-0.7	0.01-0.25

Reproduced from Matos et al, J Pediatr 1997; 131:252-257.  
Abbreviations: Ca, calcium; Cr, creatinine

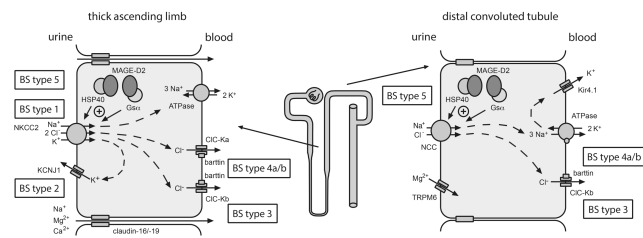


Figure 1 Pathophysiology of Bartter syndrome. Schematic model of salt transport in the thick ascending limb (TAL) and the distal convoluted tubule (DCT) with associated defects in Bartter syndrome (BS) indicated. In the TAL, NaCl is reabsorbed into by the NaK2Cl cotransporter NKCC2, mutated in BS type 1. Here, the K ion is recycled into the tubular lumen via the apical K channel KCNJ1 (ROMK), mutated in BS type 2. In the DCT, NaCl enters the tubular epithelium via the NaCl cotransporter NCC. In both tubular segments, Cl leaves the cell on the basolateral side through Cl-permeable ion channels CIC-Ka and CIC-Kb. A molecular defect of CIC-Kb causes BS type 3. Mutations in either the accessory subunit Barttin or a combined defect of both chloride channels CIC-Ka and CIC-Kb result in BS type 4a and b. Finally, transient BS type 5 is caused by mutations of MAGED2. MAGED-2 was discovered as part of a protein complex regulating NKCC2 and NCC from intracellular degradation via HSP40 and promotes apical targeting of NKCC2 and NCC via Gs-alpha<sup>35</sup>.

Aggregate evidence quality	Benefit or harm predominates	Benefit and harm balanced
<b>Level A</b> • Intervention: well-designed and conducted trials, meta-analyses on applicable populations • Diagnosis: independent gold-standard studies of applicable populations	Strong recommendation	Weak recommendation (based on balance of benefit and harm)
<b>Level B</b> Trials or diagnostic studies with minor limitations; consistent findings from multiple observational studies	Moderate recommendation	
<b>Level C</b> Single or few observational studies or multiple studies with inconsistent findings or major limitations		
<b>Level D</b> Expert opinion, case reports, reasoning from first principles	Weak recommendation (based on low-quality evidence)	No recommendation may be made
<b>Level X</b> Exceptional situations where validating studies cannot be performed and benefit or harm clearly predominates	Moderate recommendation	Strong recommendation

Figure 2 American Academy of Pediatrics grading matrix for determining the levels of evidence and strength of recommendations (Pediatrics 2004, from Haffner et al, Nat Rev Nephrol 2019).

Table 1 Molecular genetics of Bartter syndrome

	Type 1	Type 2	Type 3	Type 4a	Type 4b	Type 5
<b>OMIM</b>	601678	241200	607364	602522	613090	300971
<b>Gene</b>	SLC12A1	KCNJ1	CLCNKB	BSND	CLCNKA + CLCNKB	MAGED2
<b>Protein</b>	NKCC2	KCNJ1 (ROMK or Kir1.1)	CIC-Kb	Barttin	CIC-Ka + CIC-Kb	MAGED-2
<b>Inheritance</b>	AR	AR	AR	AR	AR	XLR

Abbreviations: OMIM, Online Mendelian Inheritance in Man; AR, autosomal recessive; XLR, X-linked recessive

Table 4 Differential diagnosis of Bartter syndrome

Leading symptom	Differential diagnosis	Additional findings
<b>Polyhydramnios of fetal origin</b>	Aneuploidia Gastrointestinal tract malformation Congenital chloride diarrhea	Abnormal karyotype Variable, empty stomach  Dilated intestinal loops
<b>Salt loss</b>	Pseudohypoaldosteronism type I	Metabolic acidosis, hyperkalemia
<b>Salt loss with hypokalemic alkalosis</b>	Congenital chloride diarrhea Pseudo-Bartter syndrome, e.g. in CF Gitelman syndrome  HNF1B nephropathy  HELIX syndrome  Autosomal dominant hypocalcemia EAST/SeSAME syndrome Surreptitious vomiting Surreptitious laxative use Surreptitious diuretic use	Low urinary chloride  Low urinary chloride  Hypocalciuria, hypomagnesemia Renal malformation, cysts, MODY5, hypomagnesemia Hypercalcemia, hypohidrosis, ichthyosis Hypocalcemia, seizures  Ataxia, seizures, developmental delay Low urinary chloride Low urinary chloride Highly variable urinary chloride
<b>Hypokalemic alkalosis without salt loss</b>	Primary hyperaldosteronism Apparent mineralocorticoid excess Liddle syndrome	Hypertension, low renin  Hypertension, low renin/aldosterone Hypertension, low renin/aldosterone
<b>Nephrocalcinosis</b>	Distal renal tubular acidosis Proximal tubular defects Familial hypomagnesemia/hypercalciuria Apparent mineralocorticoid excess	Metabolic acidosis  No metabolic alkalosis No hypokalemic metabolic alkalosis Hypertension, low renin/aldosterone

Abbreviations: CF, cystic fibrosis

Table 5 Web resources for patients with Bartter syndrome

Country/Region	Weblinks
Belgium	<a href="http://www.airg-belgique.org">http://www.airg-belgique.org</a>
Europe	<a href="http://www.federg.org">http://www.federg.org</a> <a href="http://www.erknet.org">http://www.erknet.org</a>
France	<a href="https://www.airg-france.fr">https://www.airg-france.fr</a>
Germany	<a href="http://www.orpha.net/static/DE/barttersyndrom.html">http://www.orpha.net/static/DE/barttersyndrom.html</a> <a href="https://www.rehakids.de">https://www.rehakids.de</a>
Italy	<a href="http://www.iss.it/cnmr">http://www.iss.it/cnmr</a> <a href="https://associazionebarttergitelman.weebly.com">https://associazionebarttergitelman.weebly.com</a>
The Netherlands	<a href="http://niertube.nl">http://niertube.nl</a> <a href="http://nieren.nl/Bartter">http://nieren.nl/Bartter</a>
UK	<a href="https://rarerenal.org/patient-information/">https://rarerenal.org/patient-information/</a> <a href="https://rarerenal.org/rare-disease-groups/hypokalaemic-alkaloses-rdg/">https://rarerenal.org/rare-disease-groups/hypokalaemic-alkaloses-rdg/</a>
USA	<a href="https://rarediseases.org/rare-diseases/bartters-syndrome/">https://rarediseases.org/rare-diseases/bartters-syndrome/</a> <a href="http://barttersite.org">http://barttersite.org</a>

Table 6 Sick day rules for patients with Bartter syndrome

Do not stop taking your medication unless advised by your doctor

Get your potassium and acid base status checked as soon as possible if you feel unwell for any reason

If you have diarrhea or vomiting, increase your fluid intake but ensure that you add a pinch of salt, or some electrolyte powder, to anything you drink

If you are vomiting and cannot keep anything down for 24 hours or more, you should seek immediate medical advice and hold medications, such as indomethacin, ibuprofen or celecoxib

Also, seek immediate medical advice if you pass out/faint, or:

- become dizzy
- develop tingling or muscle weakness
- notice an irregular heartbeat (palpitations)
- have painful muscle spasms

and cannot relieve these symptoms with extra salt/potassium supplements

See your doctor if you notice any unusual symptoms, as your medication dosage might need altering; a simple blood test may be all that is needed

Don't forget that your medication (indomethacin, ibuprofen) prevents fever and may thus mask the severity of infectious diseases (e.g. pneumonia)

Adapted from Blanchard et al, Kidney Int 2017



## BOX 1 RECOMMENDATIONS FOR DIAGNOSIS OF BARTTER SYNDROME

### A. Prenatal period

- During pregnancy, a diagnosis of (antenatal) Bartter syndrome (BS) should be considered in the presence of a polyhydramnios of fetal origin (grade C, weak recommendation)
- We do not recommend the assessment of electrolytes and/or aldosterone from amniotic fluid for prenatal diagnosis of BS (grade C, moderate recommendation)
- Molecular genetic testing can be applied for prenatal diagnosis, however, recommendations should be adapted to country-specific ethical and legal standards and communicated using appropriated genetic counseling (grade D, weak recommendation)
- Whenever genetic testing is unavailable, the assessment of the “Bartter index” (AFP x total protein) in the amniotic fluid might be considered for prenatal diagnosis of BS (grade C, weak recommendation)

### B. Postnatal period

- Postnatally, a diagnosis of BS should be considered in the presence of renal salt wasting, polyuria, rapid weight loss, and signs of dehydration. Failure to thrive, recurrent vomiting, repeated fever, hypochloremic and hypokalemic metabolic alkalosis and nephrocalcinosis should raise the suspicion of BS beyond the neonatal period (grade C, moderate recommendation)
- For initial diagnostic work-up, we recommend the following (grade C, moderate recommendation)
  - Evaluation of past medical history including polyhydramnios, premature birth, growth failure, and family history
  - Biochemical parameters: serum electrolytes (sodium, chloride, potassium, calcium, magnesium), acid-base status, renin, aldosterone, creatinine, fractional excretion of chloride, and urinary calcium/creatinine ratio
  - Renal ultrasound to detect medullary nephrocalcinosis and/or kidney stones
- We recommend confirming the clinical diagnosis of BS by genetic analysis whenever possible (grade B, moderate recommendation)
- We suggest offering genetic counseling for families with probands with confirmed clinical and/or genetic diagnosis of BS (grade D, weak recommendation)
- We do not recommend tubular function tests with furosemide or thiazides for patients with suspected BS whenever genetic testing is accessible (grade D, moderate recommendation)

## BOX 2 RECOMMENDATIONS FOR THERAPY OF BARTTER SYNDROME

### A. Prenatal period

- Before the initiation of therapeutic measures (repeated amniocentesis and/or nonsteroidal antiinflammatory drugs (NSAIDs)) aiming at the reduction of amniotic fluid volume we suggest to carefully weigh the intended benefit (prolongation of pregnancy) with the potential risks for the fetus, such as premature closure of the ductus arteriosus or necrotizing enterocolitis (grade D, weak recommendation)
- Whenever prenatal therapy for the reduction of amniotic fluid is considered, we suggest involving a multidisciplinary team including a maternal-fetal medicine specialist, a neonatologist, pediatric nephrologist and a pediatric cardiologist (in case of NSAID therapy) (grade D, weak recommendation)

### B. Postnatal period

- We recommend considering pharmacological doses (5-10 mmol/kg/d) of sodium chloride supplementation in patients with BS (grade C, moderate recommendation)
- We do not recommend salt supplementation in patients with BS and secondary nephrogenic diabetes insipidus (grade D, weak recommendation)
- We recommend using potassium chloride, if potassium is supplemented (grade C, moderate recommendation)
- We do not recommend aiming for complete normalization of plasma potassium levels (grade D, weak recommendation)
- Whenever needed, we recommend using oral magnesium supplements, at best organic magnesium salts because of their better bioavailability (grade D, weak recommendation)
- We recommend spreading out salt and electrolyte supplements throughout the day, as much as possible (grade C, moderate recommendation)
- We recommend considering treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) in symptomatic patients with BS, especially in early childhood (grade B, moderate recommendation)
- We recommend using gastric acid inhibitors together with non-selective cyclooxygenase inhibitors (grade C, moderate recommendation)
- We suggest optimizing nutritional support to facilitate optimal growth (grade D, weak recommendation)
- We do not recommend routine use of potassium-sparing diuretics, ACE inhibitors or angiotensin receptor blockers in BS (grade D, weak recommendation)
- We do not recommend the use of thiazides to reduce hypercalciuria in BS (grade D, weak recommendation)

## BOX 3 RECOMMENDATIONS FOR FOLLOW-UP OF PATIENTS WITH BARTTER SYNDROME

### A. Frequency and setting of visits

- We suggest that patients with BS should be followed in specialized centers with experience in renal tubular disorders to facilitate best medical care (grade D, weak recommendation)
- We suggest that infants and young children with BS should be seen at least every 3-6 months, depending on severity of clinical problems, to ensure adequate metabolic control, growth and psychomotor development (grade C, weak recommendation)
- We suggest that older children with an established therapy and stable condition should be seen at least every 6-12 months (grade C, weak recommendation)
- We suggest that adult patients should be seen every 6-12 months (grade C, weak recommendation)
- We suggest evaluating quality of life (QoL) using age-appropriate QoL scales if available from aged 5 years onwards at 2 yearly intervals (grade D, weak recommendation)

### B. Follow-up of children

- At each follow-up visit, we suggest to focus history and examination on dehydration, degree of polyuria, signs of muscular weakness, growth and psychomotor development (grade C, weak recommendation)
- We suggest that biochemical workup should include acid base status (either by blood gas or by measurement of venous total CO<sub>2</sub>), serum electrolytes (including bicarbonate, chloride, magnesium), renal function, PTH and urinary calcium excretion (grade C, weak recommendation)
- We suggest to assess urine osmolality to test for secondary NDI (grade C, weak recommendation)
- We suggest performing renal ultrasound at least every 12-24 months to monitor nephrocalcinosis, the occurrence of kidney stones, and signs of secondary obstructive uropathy (grade C, weak recommendation)
- For children with growth retardation despite intensified efforts at metabolic control (optimization of NSAID and salt supplementation including potassium chloride), we suggest to consider growth hormone deficiency (grade C, weak recommendation)

### C. Follow-up of adults

- At each follow-up visit, we suggest to focus history and examination on dehydration, degree of polyuria, signs of muscular weakness, fatigue and palpitations (grade C, weak recommendation)
- We suggest that biochemical workup should include acid base status (either by blood gas or by measurement of venous total CO<sub>2</sub>), serum electrolytes (including bicarbonate, chloride, magnesium), renal function, PTH, urinary calcium excretion, and microalbuminuria (grade C, weak recommendation)
- We recommend performing renal ultrasound at least every 12-24 months to monitor nephrocalcinosis, the occurrence of kidney stones, and signs of secondary obstructive uropathy (grade C, weak recommendation)
- We suggest performing further cardiology workup in patients complaining of palpitations or syncope (grade C, weak recommendation)
- For pregnant women or those planning to become pregnant, we suggest the timely institution of