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# Diagnosis and management of Bartter syndrome: executive summary of the consensus and recommendations from the European Rare Kidney Disease Reference Network Working Group for Tubular Disorders

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**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 defective salt reabsorption predominantly in the thick ascending limb of the loop of Henle. There is significant variability in the clinical expression of the disease, which is genetically heterogenous 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 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 and propose clinical indicators to assess and improve quality of care.**

*Kidney International* (2021) **99**, 324–335; <https://doi.org/10.1016/j.kint.2020.10.035>

**KEYWORDS:** Bartter syndrome; hypokalemic metabolic alkalosis; inherited hypokalemia; salt-losing tubulopathy

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Received 3 July 2020; revised 30 September 2020; accepted 29 October 2020

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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 (BS1–5), based on molecular genetics, have been identified to date (Table 1).<sup>1</sup>

Clinical characteristics include polyuria, dehydration, failure to thrive, growth retardation, and a medical history of polyhydramnios with premature birth. Hypercalciuria and nephrocalcinosis are typical for some forms. BS is a potentially life-threatening condition necessitating rapid diagnosis and therapy.

The primary molecular defect in all types of BS leads to impaired salt reabsorption in the thick ascending limb of the loop of Henle.<sup>2</sup> Regardless of the underlying molecular defect, mutations result in renal tubular salt wasting with activation of the renin-angiotensin system and 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 prostaglandin E<sub>2</sub>), which in turn stimulate renin secretion and aldosterone production, in the attempt to reestablish

**Table 1 | Molecular genetics of Bartter syndrome**

Characteristic	Type 1	Type 2	Type 3	Type 4a	Type 4b	Type 5
OMIM	601678	241200	607364	602522	613090	300971
Gene	<i>SLC12A1</i>	<i>KCNJ1</i>	<i>CLCNKB</i>	<i>BSND</i>	<i>CLCNKA + CLCNKB</i>	<i>MAGED2</i>
Protein	NKCC2	KCNJ1 (ROMK or Kir1.1)	CIC-Kb	Barttin	CIC-Ka + CIC-Kb	MAGE-D2
Inheritance	AR	AR	AR	AR	AR	XLR

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

normal intravascular volume and glomerular perfusion.<sup>3</sup> In BS, the tubuloglomerular feedback is uncoupled because chloride is not reabsorbed in the macula densa owing to the underlying molecular defects. Therefore, cells produce high amounts of prostaglandin E<sub>2</sub> regardless of volume status, causing excessive synthesis of renin and aldosterone. This constitutes the rationale for treating BS patients with prostaglandin synthesis inhibitors, which often results in noticeable clinical improvement.<sup>4–6</sup>

Impaired salt reabsorption in the thick ascending limb has 2 additional consequences that are important in BS, namely (i) a reduction of calcium reabsorption with hypercalciuria and progressive medullary nephrocalcinosis,<sup>7,8</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>9</sup> An exception is seen in 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), encoding proteins directly involved in salt reabsorption in the thick ascending limb (BS1–4) or regulating their expression (BS5). The mode of inheritance is autosomal recessive in BS1–4<sup>10–14</sup> and X-linked recessive in BS5.<sup>15</sup>

Clinical characteristics, such as severity of biochemical abnormalities, presence of polyhydramnios and preterm delivery, degree of calciuria with or without medullary nephrocalcinosis, and presence of sensorineural deafness show typical gene-specific patterns. Several patients with BS3 have clinical features that are virtually indistinguishable from Gitelman syndrome (GS), another salt-losing tubulopathy.<sup>1</sup>

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 glomerular filtration rate. In addition, nonsteroidal antiinflammatory drugs (NSAIDs) are for most patients a mainstay of treatment,<sup>16</sup> at least during the first years of life (except in transient BS5). The use of other therapies, such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, have been reported in the literature, but evidence supporting their efficacy, tolerability, and safety is 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 relationship 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 cardiac arrhythmias. Other open questions include optimal diagnostic approaches, particularly in the neonatal period, and the best therapeutic strategies based on outcome data. Also, the best management of BS during pregnancy has not been established.

Therefore, an interdisciplinary group of experts was assembled under the umbrella of the European Rare Kidney Disease Reference Network to develop recommendations for the diagnosis and management of patients with BS (for full version, see Konrad *et al.*<sup>17</sup>). The recommendations are listed in Boxes 1–3. It is beyond the scope of this executive summary to discuss each recommendation in detail. Instead, we highlight the significant underlying concepts. The recommendations are endorsed by the European Society for Paediatric Nephrology and the Working Group on Inherited Kidney Disorders of the European Renal Association–European Dialysis and Transplantation Association.

## METHODS

The consensus process was initiated by European Rare Kidney Disease Reference Network. Two groups were assembled: a consensus core group and a voting panel. The core group comprised specialists for pediatric and adult nephrology, genetics, and obstetrics and a patient representative. The voting group included 36 members with special expertise in Bartter syndrome.

The core group performed a systematic literature review via the PubMed and Cochrane databases through October 15, 2018. The following key MeSH terms were used: Bartter syndrome, inherited hypokalemic alkalosis, *SLC12A1*, *KCNJ1*, *CLCNKA*, *CLCNKB*, *BSND*, and *MAGED2*. The search retrieved 2218 results, and 135 articles were referenced in the full version.<sup>17</sup>

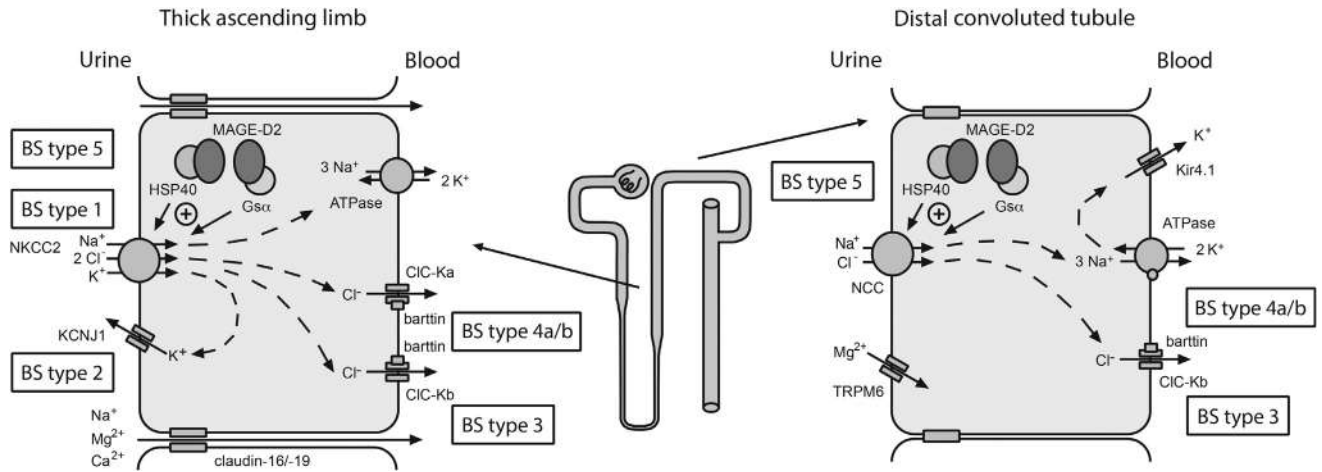
Initial recommendations were developed during a first meeting by discussion in thematic workgroups and plenary sessions. Evidence and recommendations were graded (whenever possible) according to the method used in the current American Academy of Pediatrics guidelines.<sup>18,19</sup> A first written draft was compiled and reviewed by the consensus core group. Remaining gaps were identified by a second meeting. Consequently, 2 rounds of anonymous voting were performed using the Delphi method until at least 70% support was reached for each individual recommendation.

## Diagnosis

See Box 1. For details, see Konrad *et al.*<sup>17</sup>

## General approach

The diagnosis of BS is primarily based on clinical, biochemical and sonographic findings (Box 1). Even if the different subtypes of BS



**Figure 1 | Pathophysiology of Bartter syndrome.** Schematic model of salt transport in the thick ascending limb and the distal convoluted tubule with associated defects in Bartter syndrome (BS) indicated. In the thick ascending limb, NaCl is reabsorbed by the NaK2Cl cotransporter NKCC2, which is mutated in BS type 1. Here, the potassium ion is recycled into the tubular lumen via the tubular potassium channel KCNJ1 (ROMK), which is mutated in BS type 2. In the distal convoluted tubule, NaCl enters the tubular epithelium via the NaCl cotransporter NCC. In both tubular segments, chloride leaves the cell on the basolateral side through chloride-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 types 4a and 4b. Finally, transient BS type 5 is caused by mutations of MAGE-D2. MAGE-D2 stimulates trafficking of NKCC2 and NCC from intracellular degradation via HSP40 and promotes apical targeting of NKCC2 and NCC via Gs-alpha.<sup>20</sup>

can usually be characterized clinically (Table 2<sup>20,21</sup>), we recommend genetic analysis for confirmation.

**Antenatal diagnostic work-up**

Early polyhydramnios of fetal origin should raise the clinical suspicion of BS. In principle, there are 2 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.

However, whenever prenatal diagnosis is indicated, we consider genetic testing to be the most reliable method. In situations, where prenatal genetic testing is not available or diagnostic, the assessment of the “Bartter index” (total protein × alfa-fetoprotein) may be considered.<sup>22</sup> In larger studies, other parameters, such as high chloride or aldosterone levels, failed to distinguish between amniotic fluid from polyhydramnios related to other causes and control pregnancies.<sup>23,24</sup>

**Postnatal diagnostic work-up**

The diagnostic work-up for BS after birth should include a detailed clinical evaluation asking for a family history of pregnancy complicated by polyhydramnios with or without premature birth, and a 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, muscle weakness, low blood pressure, and pubertal delay.

Laboratory analysis for suspected BS should include the parameters listed in Box 1. The assessment of urinary prostaglandin excretion (prostaglandin E<sub>2</sub>) may be helpful, although this procedure is not feasible in a routine clinical setting. For definitive diagnosis, we recommend genetic testing.

**Clinical characteristics of different types of BS**

Key clinical and biochemical findings in patients with BS are detailed below and in Table 2, with a special focus on gene-

specific differences between the known subtypes of BS. For differential diagnosis, see the Differential Diagnosis section below.

**Age at presentation.**

- BS causes polyhydramnios, leading to premature birth in the majority of patients.
- Polyhydramnios typically develops between the 20th and 30th weeks of gestation. Timing and severity vary according to the underlying genetic defect. In BS4 and BS5, polyhydramnios is typically observed earlier than in BS1 and BS2.<sup>15,20,21,25</sup>
- BS5 always presents antenatally, but symptoms spontaneously resolve typically around the estimated date of delivery.
- BS3 usually manifests later in life. Nevertheless, a prenatal presentation does not exclude BS3. The vast majority of patients with BS3 are diagnosed after the age of 1 year.<sup>26–32</sup> Patients typically present with failure to thrive, poor weight gain, or polyuria with polydipsia. Less frequent symptoms are related to dehydration. Most patients exhibit salt craving, although this is rarely a presenting symptom.
- In a minority of cases, the diagnosis of BS is incidental after noticing abnormal laboratory results, discovery of nephrocalcinosis, or family screening.

**Salt wasting, plasma potassium, chloride, magnesium, and bicarbonate levels.**

- After birth, the first symptom is often hypovolemia from renal salt loss.
- Hypochloremic and hypokalemic metabolic alkalosis may not be present during the first days of life.
- Infants with BS2 often have transient neonatal acidosis and hyperkalemia and, on average, hypokalemia and alkalosis are less pronounced during follow-up.
- In contrast, patients with BS3 and BS4 tend to have the lowest plasma potassium levels and the most pronounced hypochloremic alkalosis.
- In some patients with BS3, hypomagnesemia may be present.

**Box 1 | Recommendations for diagnosis of Bartter syndrome****Prenatal period**

- During pregnancy, a diagnosis of (antenatal) 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 with appropriate genetic counseling (grade D, weak recommendation).
- Whenever genetic testing is unavailable, the assessment of the “Bartter index” (AFP × total protein) in the amniotic fluid might be considered for prenatal diagnosis of BS (grade C, weak recommendation).

**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 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 means of 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 if genetic testing is accessible (grade D, moderate recommendation).

AFP, alpha fetoprotein; BS, Bartter syndrome.

**Calciuria and nephrocalcinosis.**

- Hypercalciuria with subsequent nephrocalcinosis occurring after 1–2 months of life is a typical feature of BS1 and BS2. Although computerized tomography 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 which may occur in rare cases in BS.
- In contrast, patients with BS3 and BS4 usually have normocalciuria, although hypercalciuria may occur.
- Interestingly, hypocalciuria has also been reported in patients with BS3, and these patients mimic the phenotype of GS.
- In transient BS5, hypercalciuria may be observed, but nephrocalcinosis is a rare finding.

**Genetic testing.**

- We recommend offering genetic testing with the use of a gene panel to all patients with a clinical suspicion of BS. Recommendations for genes to be included in the panel are detailed in Table 3.
- The detection of pathogenic variants in genes responsible for BS is crucial to confirm the clinical diagnosis and for genetic counseling.
- An early genetic diagnosis may help in resolving difficult cases with overlapping phenotypes. 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 in transient BS5.
- Analytical sensitivity in BS is 90%–100%, and clinical sensitivity is ~75% in children<sup>21,27,33</sup> but only 12.5% in adult patients.<sup>34</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 because the analysis of *CLCNKB* is technically challenging.

- Although large rearrangements can be detected by next-generation sequencing, it is recommended to confirm them by a second independent method (e.g., multiplex ligation-dependent probe amplification). Large rearrangements are particularly frequent in the *CLCNKB* gene but have also been described in *KCNJ1*, *BSND*, and *MAGED2*.<sup>13,21,35</sup>
- Genetic counseling should be offered to any family affected by BS. Counseling should include cascade screening. 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 counseling and may be considered on an individual basis, according to national ethical and legal standards.

**DIFFERENTIAL DIAGNOSIS**

- The differential diagnosis of BS depends on the age at presentation and the specific context (Table 4; for details, see Konrad *et al.*<sup>17</sup>).
- Polyhydramnios due to excessive fetal polyuria is virtually always caused by BS. There are no reports of other inherited tubular disorders causing severe polyhydramnios. In particular, polyhydramnios is not 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 harbor *KCNJ1* mutations underlying BS2.<sup>27,36</sup>



**Table 2 | Main clinical and biochemical characteristics of different types of Bartter syndrome**

Characteristic	Type 1	Type 2	Type 3	Type 4a	Type 4b	Type 5
Age at onset	Prenatally Severe	Prenatally Severe	0–5 years	Prenatally Severe	Prenatally Severe	Prenatally Very severe
Polyhydramnios			Absent or mild			
Gestational age at birth, wks, median (IQR)	32 (29–34)	33 (31–35)	37 (36–41)	31 (28–35)	31 (28–35)	29 (21–37)
Leading symptoms	Polyuria, hypochloremia, alkalosis, hypokalemia	Polyuria, hypochloremia, alkalosis, transient neonatal hyperkalemia	Hypokalemia, hypochloremia, alkalosis, failure to thrive	Polyuria, hypochloremia, alkalosis, hypokalemia	Polyuria, hypochloremia, alkalosis, hypokalemia	Polyuria, hypochloremia, alkalosis, hypokalemia
Calcium excretion	High	High	Variable	Variable	Variable	High
Nephrocalcinosis	Very frequent	Very frequent	Rare, mild	Rare, mild	Rare, mild	Rare, mild
Plasma Cl/Na ratio	Normal	Normal	Decreased	Decreased	Decreased	Increased
Other findings			Mild hypomagnesemia	Deafness, risk for CKD, ESRD	Deafness, risk for CKD, ESRD	Large for gestational age, transient disease

CKD, chronic kidney disease; ESRD end-stage renal disease; IQR, interquartile range. Data from Komhoff and Laghmani<sup>20</sup> and Legrand et al.<sup>21</sup>

- Congenital chloride diarrhea can be confused with BS. Pregnancies are often complicated by polyhydramnios with preterm delivery (usually not severe).<sup>37</sup> Postnatally, this disease causes pronounced hypokalemic and hypochloremic metabolic alkalosis secondary to watery diarrhea.
- Pseudo-Bartter syndrome is occasionally observed in cystic fibrosis because of salt loss in sweat.
- Presentation beyond infancy, especially in adolescence or even adulthood (most often BS3), makes GS a primary consideration in those patients with hypocalciuria and/or hypomagnesemia. Patients with hepatocyte nuclear factor 1β nephropathy may also present with hypokalemic alkalosis and hypomagnesemia.<sup>38</sup> Other rare tubulopathies exhibiting metabolic alkalosis are listed in Table 4.
- Some patients with BS primarily present with nephrocalcinosis and/or urolithiasis. A young age at onset of kidney stone disease should raise the clinical suspicion of a specific underlying cause, including (incomplete) distal renal tubular acidosis.
- If the presenting sign is hypokalemia, the initial differential diagnosis is wide. In this context, it is important to distinguish renal from gastrointestinal potassium loss and potassium shifts. If primary hyperaldosteronism and diuretic and/or laxative use or abuse are excluded, the differential diagnosis narrows down to rare tubulopathies (Table 4).
- Urinary chloride excretion assessed by either fractional chloride excretion or urinary sodium/chloride ratio is helpful to distinguish renal from extrarenal salt losses. In BS, fractional chloride excretion is usually elevated (>0.5%).<sup>32</sup>

In theory, thick ascending limb and distal convoluted tubule function can be clinically tested by administering loop diuretics or thiazides to better characterize the clinical diagnosis of BS. Diuretic tests, however, are obsolete because they have been surpassed by genetic analysis. It is important to note that there is a potential risk of severe volume depletion in subjects with suspected BS, especially in infancy, because of an exaggerated response to thiazides due to the compensatory up-regulation of salt reabsorption in the distal convoluted tubule.<sup>39</sup> Moreover, there remain significant uncertainties about their diagnostic value.<sup>39–41</sup> We therefore advise against routine tubular function testing in patients with BS, in line with the Kidney Disease: Improving Global Outcomes consensus statement on GS.<sup>42</sup> Nevertheless, these tests may have a role in individual challenging cases or for research purposes, together with genetic testing, if performed in experienced (tertiary) medical centers.

**THERAPY**

See Box 2. For details, Konrad et al.<sup>17</sup>

**Prenatal therapy**

- Pregnancies complicated by polyhydramnios are at risk of adverse outcomes, especially preterm delivery and complications of premature birth.<sup>43,44</sup> Serial amniocenteses are commonly used in the intention of prolonging pregnancies, but the benefits of this strategy have not been evaluated in prospective studies.

**Table 3 | Genes recommended to be included in genetic testing for Bartter syndrome**

Gene	Associated disorder (MIM)
<i>SLC12A1</i> <sup>a</sup>	BS1 (601678)
<i>KCNJ1</i> <sup>a</sup>	BS2 (241200)
<i>CLCNKB</i> <sup>a</sup>	BS3 (607364)
	BS4b (613090)
<i>CLCNKA</i> <sup>a</sup>	BS4b (613090)
<i>BSND</i> <sup>a</sup>	BS4a (602522)
<i>MAGED2</i> <sup>a</sup>	BS5 (300971)
<i>SLC12A3</i> <sup>a</sup>	Gitelman (263800)
<i>CASR</i>	ADH (601198)
<i>KCNJ10</i>	EAST/Sesame (612780)
<i>SLC26A3</i>	CCD (214700)
<i>CLDN10</i>	HELIX (617671)
<i>SCNN1A</i>	PHA1B (264350)
<i>SCNN1B</i>	Liddle syndrome (177200)
<i>SCNN1G</i>	
<i>NR3C2</i>	PHA1A (177735)
<i>HSD11B2</i>	AME (218030)
<i>CYP11B1</i>	HALD1 (103900)
<i>CLCN2</i>	HALD2 (605635)
<i>KCNJ5</i>	HALD3 (600734)
<i>CACNA1H</i>	HALD4 (607904)

ADH, autosomal dominant hypocalcemia; AME, apparent mineralocorticoid excess; BS, Bartter syndrome; CCD, congenital chloride diarrhea; EAST, epilepsy, ataxia, sensorineural deafness, tubulopathy; HALD, familial hyperaldosteronism; HELIX, hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, xerostomia; MIM, Mendelian Inheritance in Man; PHA, pseudohypoaldosteronism.

<sup>a</sup>Genes in rows 2–8 should be included in a minimal diagnostic panel, i.e., the genes underlying BS, as well as Gitelman syndrome, which can be difficult to distinguish clinically from BS3. The remaining list also includes genes, which can have phenotypic overlap with BS. BS2 can mimic pseudohypoaldosteronism type 1 (PHA1) in the neonatal period. The listed hypertensive disorders can biochemically mimic BS.

Listed are genes to be considered in the (differential) diagnosis of BS and therefore should be included in a panel of genes for genetic testing.

- Maternal treatment with NSAIDs can be considered. Apparent efficacy has been reported in individual cases of polyhydramnios secondary to different causes and in idiopathic polyhydramnios.<sup>45</sup> However, the treatment carries significant risks for the fetus, especially of fetal ductus arteriosus constriction. Therefore, close monitoring with the use of fetal echocardiography is mandatory in all cases of maternal NSAID therapy. Other reported complications include neonatal intestinal perforation and necrotizing enterocolitis.<sup>45</sup>

To date, only a few cases of BS with positive outcome after serial amniocentesis and/or prenatal indomethacin therapy have been reported.<sup>46–49</sup> A substantial publication bias toward favorable outcomes cannot be excluded.

Given the above-mentioned risks and lack of prospective studies, a formal recommendation cannot be made.

- If prenatal intervention is considered, 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.

- Supplementation with sodium chloride constitutes a physiologic treatment that can support extracellular volume and improve electrolyte abnormalities. At least 5–10 mmol/kg/

**Table 4 | Differential diagnosis of Bartter syndrome**

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

CF, cystic fibrosis; CKD, chronic kidney disease; EAST, epilepsy, ataxia, sensorineural deafness, tubulopathy; HELIX, hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, xerostomia; HNF1B, hepatocyte nuclear factor 1 beta; MODY5, maturity onset diabetes of the young type 5; SeSAME, seizures, sensorineural deafness, ataxia, mental retardation, electrolyte imbalance.

d has been recommended.<sup>50</sup> Beyond infancy, some of this supplementation may be provided by salt craving and high spontaneous salt intake that is typical for BS.

- Some patients with BS1 and BS2 have a secondary form of nephrogenic diabetes insipidus.<sup>51,52</sup> These patients present a therapeutic dilemma as salt supplementation would 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.<sup>32</sup> Potassium salts (e.g., citrate) should be avoided because they potentially worsen the metabolic disturbance by aggravating the alkalosis.

Hypokalemia in BS can be associated with severe complications, including paralysis, rhabdomyolysis, cardiac

**Box 2 | Recommendations for therapy of Bartter syndrome****Prenatal period**

- Before the initiation of therapeutic measures (repeated amniocentesis and/or NSAIDs) aiming at the reduction of amniotic fluid volume, we suggest carefully weighing 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, neonatologist, pediatric nephrologist, and pediatric cardiologist (in case of NSAID therapy) (grade D, weak recommendation).

**Postnatal period**

- We recommend considering pharmacologic 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 owing to 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 NSAIDs in symptomatic patients with BS, especially in early childhood (grade B, moderate recommendation).
- We recommend using gastric acid inhibitors together with nonselective 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).

ACE, angiotensin-converting enzyme; BS, Bartter syndrome; NSAID, nonsteroidal anti-inflammatory drug.

rhythm abnormalities, and sudden death.<sup>53–55</sup> The following recommendation, made for GS,<sup>42</sup> applies equally to BS: Potassium chloride 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). Potassium-rich food should be advised, with the caution that some of them contain high amounts of carbohydrates and calories. The target level for plasma potassium is not exactly known, but a reasonable target level may be 3.0 mmol/l. In GS as well, a level of 3.0 mmol/l has been suggested with the explicit acknowledgement that this may not be achievable in some patients.<sup>42</sup> 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. It is important to note that organic salts (e.g., aspartate, citrate, lactate) have a higher bioavailability than magnesium oxide or hydroxide.<sup>56</sup> Exact target levels for plasma magnesium in BS are unknown but a level >0.6 mmol/l appears to be reasonable.

Because urinary salt and electrolyte losses are continuous, ideal supplementation would be as close to continuous as possible. Infrequent large doses of supplementation will cause rapid changes in blood levels depending on timing of the sample in relation to the last dose. 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.

**NSAIDs.**

- Pharmacologic suppression of prostaglandin formation addresses the underlying pathophysiology, and multiple clinical observational studies have shown benefit in the form of improved growth and electrolyte profile.<sup>57–60</sup> The use of selective COX-2 inhibitors has also been reported in BS.<sup>6,61–63</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 doses), and celecoxib (2–10 mg/kg/d in 2 doses).
- Currently, there is insufficient evidence to recommend 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 necrotizing enterocolitis should be carefully considered. Euvolemia should be achieved before initiating NSAIDs, because volume status may affect the potential nephrotoxicity.
- Extended use of NSAIDs for pain is strongly associated with chronic kidney disease.<sup>64</sup> Whether this also applies to patients with BS has been disputed.<sup>65,66</sup> Indeed, commencement of NSAIDs in BS typically results in clinical

**Box 3 | Recommendations for follow-up of patients with Bartter syndrome****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 QoL using age-appropriate scales from age 5 years onward at 2-year intervals (grade D, weak recommendation).

**Follow-up of children**

- At each follow-up visit, we suggest focusing the history and examination on dehydration, degree of polyuria, signs of muscular weakness, growth, and psychomotor development (grade C, weak recommendation).
- We suggest that biochemical work-up should include acid-base status (either by blood gas or by measurement of venous total CO<sub>2</sub>), serum electrolytes (including bicarbonate, chloride, and magnesium), renal function, PTH, and urinary calcium excretion (grade C, weak recommendation).
- We suggest assessing 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 for metabolic control (optimization of NSAID and salt supplementation including potassium chloride), we suggest considering growth hormone deficiency (grade C, weak recommendation).

**Follow-up of adults**

- At each follow-up visit, we suggest focusing the history and examination on dehydration, degree of polyuria, signs of muscular weakness, fatigue, and palpitations (grade C, weak recommendation).
- We suggest that biochemical work-up should include acid-base status (either by blood gas or by measurement of venous total CO<sub>2</sub>), serum electrolytes (including bicarbonate, chloride, and 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 work-up 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 a joint management plan involving nephrology and obstetrics (grade C, weak recommendation).

BS, Bartter syndrome; NDI, nephrogenic diabetes insipidus; NSAID, nonsteroidal antiinflammatory drug; PTH, parathyroid hormone; QoL, quality of life.

improvement, including a stable or even increased glomerular filtration rate, likely reflecting enhanced volume status.<sup>67</sup> Although chronic kidney disease is a common complication of BS, the cause is likely manifold, including premature birth and recurrent episodes of dehydration, so that the specific role of NSAIDs is difficult to determine.

- There are reports of “tolerance” to NSAIDs over time, as well as of discontinuation of NSAIDs at school age owing to a perceived lack of efficacy.<sup>32,59</sup> It is unclear whether this is related to insufficient dosing or a change in pathophysiology and whether at some point, the risks of NSAIDs may outweigh the benefits. Chronic use of NSAIDs should be considered carefully in each individual patient, and tapering or cessation may be indicated in stable patients.

**Gastric acid inhibitors.**

- Indomethacin and ibuprofen are nonselective inhibitors of COX enzymes. In contrast, celecoxib primarily inhibits COX-2. COX-1 is expressed in multiple tissues, and its inhibition is associated with potentially serious side-effects, which have also been reported in patients with BS receiving NSAIDs. Thus, if nonselective COX inhibitors are prescribed, they should be accompanied by gastric acid suppression. If proton pump inhibitors are

used, there is a small risk of proton pump inhibitor-associated hypomagnesemia that could compound renal magnesium wasting. Conversion to H<sub>2</sub> blockers or other antacids (or to a COX-2 inhibitor) is recommended in those instances.

**Supportive treatment.**

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

**K-sparing diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, thiazides.**

- The hypokalemic alkalosis of BS is generated in the collecting duct, mediated by aldosterone (reviewed by Kleta and Bockenhauer<sup>1</sup>). Consequently, K-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers can help ameliorate the electrolyte abnormalities in BS, and their use has been reported.<sup>30,32,68–70</sup> However, BS is primarily a salt-wasting disorder, and the enhanced sodium reabsorption in the collecting duct is a



key compensatory mechanism. Consequently, drugs that inhibit distal sodium reabsorption 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 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 despite maximization of routine treatment with NSAIDs and salt supplements.<sup>71</sup>

- Thiazides are occasionally used in an attempt to reduce calcium excretion. There are no data on their efficacy in BS. Moreover, compensatory salt reabsorption in the distal convoluted tubule is critical for maintenance of volume homeostasis. Thus, thiazides in BS may lead to life-threatening hypovolemia and should not be routinely administered.

#### **Growth hormone.**

- Growth failure with growth hormone (GH) deficiency in BS has been reported.<sup>28,32,72–74</sup> Whether this is an intrinsic part of the disorder or a secondary complication of altered acid-base and/or electrolyte homeostasis is unclear, but most reports of GH deficiency have concerned patients with BS3, who have the most severe metabolic abnormalities. In addition, elevated systemic prostaglandins may contribute to growth failure. In one report, GH deficiency failed to respond to recombinant human GH supplementation until treatment with a COX inhibitor was commenced.<sup>32</sup> Thus, before commencement of recombinant human GH, optimization of metabolic control should be attempted.

#### **FOLLOW-UP**

See [Box 3](#). For details, see Konrad *et al.*<sup>17</sup>

In BS, clinical and biochemical features and complications vary widely depending on the underlying molecular defect and individual patient.

- 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 in close contact with the patient's local health care provider. In addition, according to age and/or genotype, other professions might be involved such as dietitians, social workers, psychologists, endocrinologists, and otolaryngologists.
- At each follow-up visit, specific clinical features should be addressed and biochemical work-up performed ([Box 3](#)).
- In children, there is also special emphasis on growth and pubertal development.
- Adverse effects of NSAIDs should be looked for. In case of intercurrent illness, it has to be kept in mind that NSAIDs may prevent fever and thus mask the severity of infectious diseases.
- Renin and aldosterone levels may be helpful in assessing the adequacy of NSAID treatment.
- During follow-up, the routine assessment of quality of life with the use of age-specific standardized questionnaires

would be highly desirable. The first small case series in patients with salt-losing tubulopathies showed that quality of life 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>75</sup>

#### **Long-term outcomes and complications**

- Data on long-term outcomes in BS are sparse.
- Whereas nephrocalcinosis and hypercalciuria are present in the majority of patients (except BS3), the prevalence of symptomatic urolithiasis in BS appears to be relatively low.<sup>30</sup>
- Nephrotic-range proteinuria has been reported in BS patients.<sup>28,32,76</sup> When renal biopsies are performed, they often show diffuse glomerular and tubulointerstitial lesions with enlarged glomeruli and focal segmental glomerulosclerosis.<sup>30</sup>
- Chronic kidney disease is common in BS, and patients with BS1 and BS4 may have more severe chronic kidney disease progression than those with BS2 and BS3.<sup>30,65</sup> In addition to the molecular defect itself (especially in BS4), other risk factors potentially contributing to chronic kidney injury could be premature birth/low birth weight, nephrocalcinosis, chronic dehydration state, progressive proteinuria related to hyperfiltration due to renin-angiotensin system activation, and treatment with NSAIDs. In BS patients, there seems to be no correlation between serum potassium levels and estimated glomerular filtration rate.<sup>30,77</sup> Some patients progress to end-stage kidney disease, but exact data are lacking.
- A few kidney transplantations have been reported in the literature.<sup>30,78–84</sup> In all cases, electrolyte abnormalities and polyuria were corrected and recurrent disease was not observed.

#### **Cardiac work-up/anesthesia/sports**

- Hypokalemia with or without additional hypomagnesemia prolongs the QT interval, which could lead to an increased risk of ventricular arrhythmias. Isolated reports on cardiac arrhythmias, long QT interval, and sudden death have been reported in BS patients,<sup>53,85,86</sup> so electrocardiography should be performed at rest to assess rhythm and QT-interval duration. A further cardiology work-up, as previously recommended for GS,<sup>42</sup> is indicated when patients complain of palpitations or syncope (e.g., Holter, stress electrocardiography), or if electrocardiographic abnormalities persist despite attempted improvement of the biochemical abnormalities.<sup>87</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, or antiviral drugs, should be carefully considered.
- Caution should be taken when patients with BS undergo anesthesia. Hypokalemia and hypomagnesemia can

potentiate the effects of anesthetic agents, such as neuromuscular blockade during general anesthesia and adrenaline in regional blockade. However, there is no definitive evidence to suggest safe preoperative plasma potassium levels. In the general population, guidelines suggest aiming for potassium levels  $>3.0$  mmol/l (magnesium  $>0.5$  mmol/l).<sup>88</sup>

- 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 considered carefully, particularly in cases with a history of cardiac manifestations or prolonged QT interval.

### Pregnancy considerations

- During normal pregnancy, serum potassium levels decrease by 0.2–0.5 mmol/l around midgestation.<sup>9,89</sup>
- In pregnant women with BS, timely institution of a joint management plan involving nephrology and obstetrics as well as appropriate adaptations in therapy is mandatory.
- During pregnancy, the target level for plasma potassium is unknown, but a level of 3.0 mmol/l has been suggested with the explicit acknowledgement that this may not be achievable in some patients.<sup>42</sup>
- In patients with BS, the occurrence of hyperemesis gravidarum may be particularly dangerous owing to the subsequent electrolyte disturbances that may necessitate early parenteral fluid and electrolyte supplementation.
- Pregnant women with BS should be informed about increased requirements of electrolyte supplements, that renin-angiotensin system blockers are contraindicated, and that NSAIDs are discouraged during pregnancy.
- Monitoring of plasma electrolyte levels is advised during labor. Therefore, delivery in hospital might be considered to reduce risks of maternal complications. The overall outcome for women with BS and their infants described to date is favorable.<sup>90–95</sup>
- After delivery, the treatment of the mother may return to baseline supplementation.

### PATIENT EDUCATION

For details, see Konrad *et al.*<sup>17</sup>

- Disease-specific education for patients with BS and their families is highly important. Information can be provided through age-appropriate personal education, information leaflets, web-based information, patient-led forums, and patient/family group support events.
- It is vital that patients know what to do in case of emergency. “Sick day rules” may be helpful in case of intercurrent illness.
- BS itself and comorbidities resulting from extreme prematurity in a subset of BS patients can compromise school performance. Depending on the country, various measures to support these children may be available and should be used.

- Work performance may be limited in some patients, e.g., owing to muscle weakness or fatigue. Occupational therapists may assist patients in finding support for their individual situations.
- Patients may be 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.

### CONCLUSIONS 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. This highlights the need for comprehensive patient registries. As more such data become available, our knowledge of the natural history, treatment response, long-term complications, and quality of life will improve and thus directly influence patient management. We therefore anticipate that with time, the recommendations made here will need to be updated and revised.

### DISCLOSURE

All the authors declared no competing interests.

### ACKNOWLEDGEMENTS

The authors thank the European Rare Kidney Disease Reference Network (ERKNet) for launching, organizing, and funding of this initiative, including travel and housing costs for the core group members. The funder had no influence on the content of the consensus. The authors also thank Tanja Wlodkowski, Heidelberg, Germany, for her continuous support concerning the literature search and the panel voting procedures.

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