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ORIGINAL ARTICLE

Electrolyte abnormalities in cystic fibrosis: systematic review of the literature

Elisabetta Scurati-Manzoni · Emilio F. Fossali · Carlo Agostoni · Enrica Riva · Giacomo D. Simonetti · Maura Zanolari-Calderari · Mario G. Bianchetti · Sebastiano A. G. Lava

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Abstract
Background Cystic fibrosis per se can sometimes lead to hyponatremia, hypokalemia, hypochloremia or hyperbicarbonatemia. This tendency was first documented 60 years ago and has subsequently been confirmed in single case reports or small case series, most of which were retrospective. However, this issue has not been addressed analytically. We have therefore systematically reviewed and analyzed the available literature on this subject.
Methods This was a systematic review of the literature.
Results The reports included in this review cover 172 subacute and 90 chronic cases of electrolyte imbalances in patients with cystic fibrosis. The male:female ratio was 1.57. Electrolyte abnormalities were mostly associated with clinically inapparent fluid volume depletion, mainly affected patients aged ≤2.5 years, frequently tended to recur and often were found before the diagnosis of cystic fibrosis was established. Subacute presentation often included an history of heat exposure, vomiting, excessive sweating and pulmonary infection. History of chronic presentation, in contrast, was often inconspicuous. The tendency to hypochloremia, hypokalemia and metabolic alkalosis was similar between subacute and chronic patients, with hyponatremia being more pronounced ($P<0.02$) in subacute compared to chronic presentations. Subacute cases were treated parenterally; chronic ones were usually managed with oral salt supplementation. Retention of urea and creatinine was documented in 38 % of subacute cases.
Conclusions The findings of our review suggest that physicians should be aware that electrolyte abnormalities can occur both as a presenting and a recurring feature of cystic fibrosis.

Keywords Cystic fibrosis · Hypokalemia · Hyponatremia · Metabolic alkalosis

E. Scurati-Manzoni · E. F. Fossali
Pediatric Emergency Unit, De Marchi Hospital, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

E. Scurati-Manzoni · M. Zanolari-Calderari · M. G. Bianchetti · S. A. G. Lava
Integrated Department of Pediatrics, Ente Ospedaliero Cantonale Ticinese, University of Berne, Bern, Switzerland

C. Agostoni
Second Pediatric Clinic, Clinica De Marchi, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy

E. Riva
Department of Pediatrics, San Paolo Hospital, University of Milan, Milan, Italy

G. D. Simonetti · S. A. G. Lava
Pediatric Nephrology, University Children's Hospital Berne, University of Berne, Bern, Switzerland

M. G. Bianchetti (✉)
San Giovanni Hospital, 6500 Bellinzona, Switzerland
e-mail: mario.bianchetti@pediatrician.ch

Introduction

Hyponatremia, hypokalemia, hypochloremia or hyperbicarbonatemia are conditions that can be found in cystic fibrosis patients on drug treatment [1, 2]. Hyponatremia and hypokalemia can also be found in cystic fibrosis patients with diabetes mellitus, a major comorbidity of this disease. However, these electrolyte abnormalities are sometimes a consequence of the disease itself [3]. This tendency, first documented following heat exposure approximately 60 years ago [4], has subsequently been confirmed in several single case reports or small case series, most of which were retrospective. However, the subject has not been addressed analytically [3]. We therefore systematically reviewed and analyzed all available literature. Our aims were to describe in detail electrolyte abnormalities, suggest

preventive and therapeutic tools and warn physicians about the possible occurrence of electrolyte abnormalities as a presenting feature and complication of cystic fibrosis.

Methods

Between October 2012 and August 2013 we conducted a thorough computer-based search for the terms "cystic fibrosis alkalosis," "cystic fibrosis electrolyte abnormalities," "cystic fibrosis Bartter's," "cystic fibrosis dehydration," "cystic fibrosis heat exhaustion," "cystic fibrosis hypoelectrolytemia," "cystic fibrosis hypokalemia,", "cystic fibrosis hyponatremia," "cystic fibrosis inappropriate antidiuretic hormone," "cystic fibrosis pseudo-Bartter's," "cystic fibrosis salt depletion" and "cystic fibrosis SIADH" in the U.S. National Library of Medicine database and in the Web-based Google research engine. For this purpose we used the principles established by the UK Economic and Social Research Council guidance on the conduct of narrative synthesis and on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [5]. For the final analysis we exclusively selected reports available as a full-length article or as a letter, all of which included individually described cases of hyponatremia (≤134 mmol/L), hypochloremia (≤100 mmol/L), hypokalemia (≤3.4 mmol/L) or alkalosis (bicarbonatemia ≥27 mmol/L) in cystic fibrosis patients with or without a pathological increase in blood urea and creatinine values. Characteristic gastrointestinal or pulmonary findings and a persistently elevated sweat chloride concentration (≥60 mmol/L) were the prerequisites for diagnosis [3]. Studies addressing the mechanisms underlying the tendency towards the above-mentioned electrolyte abnormalities were also sought. Reports published in languages other than English, French, German, Italian, Portuguese or Spanish were excluded. If the same case was present in different publications, we considered the most complete description.

Reports of cystic fibrosis patients with electrolyte abnormalities possibly caused by drugs (especially thiazide or loop diuretics and alkalinizing agents such as calcium carbonate or sodium bicarbonate), by cystic fibrosis-related diabetes mellitus or by acute diarrhea were excluded. Patients with a medical history consistent with posthypercapnic alkalosis were also excluded [6]. The presentation was considered subacute when linked to circumstances such as hot weather, vomiting or a respiratory disease and lasted ≤14 days [7, 8]. On the contrary, the presentation was considered chronic in patients without symptoms or with symptoms that persisted >14 days [7, 8]. The following data for each case were collected: age, gender, laboratory test results, heat exposure, clinical presentation, chest infection, tendency of the electrolyte abnormalities to recur and previous diagnosis of cystic fibrosis. The genotype was not specifically addressed since in cystic fibrosis the association between the physical trait and the underlying genotype is not strong [9].

Numerical data were presented either as the median and interquartile range or as a "box and whiskers plot", categorical data were presented as relative frequency. The two-sided Wilcoxon–Mann–Whitney test and the Fisher exact test were performed for analysis. Significance was assumed when P was<0.05.

Research results

The flowchart of the literature research process (Fig. 1) indicates that the initial research resulted in the identification of 408 publications of which 228 remained after duplicates (i.e. publications found with two or more research terms) were excluded. Of these 228 publications, 168 were reviewed in detail and 70 were retained for the final analysis. Thirty-one reports relevant to the subject were found in the references of these latter 70 reports. Hence, a total of 101 reports published between 1951 and 2013 were included in the final analysis [4, 7, 8, 10–107]: 88 in English [4, 7, 8, 10–94], six in Spanish [95–100], three in German [101–103], two in French [104, 105] and two in Portuguese [106, 107]. They had been reported from the following countries: Arab Emirates (N=1), Argentina (N=1), Australia (N=4), Austria (N=1), Belgium (N=2), Brazil (N=2), Canada (N=6), Chile (N=3), China (N=1), Cuba (N=1), Egypt (N=1), France (N=5), Germany (N=3), Great Britain (N=9), Greece (N=2), India (N=1), Iran (N=1), Italy (N=3), Jordan (N=1), Kuwait (N=1), Lebanon (N=1), Nepal (N=1), Panama (N=1), Puerto Rico (N=1), Peru (N=1), Saudi Arabia (N=1), Serbia (N=2), Spain (N=5), Sweden (N=1), Switzerland (N=5), Thailand (N=2), Turkey (N=7), United States of America (N =24).

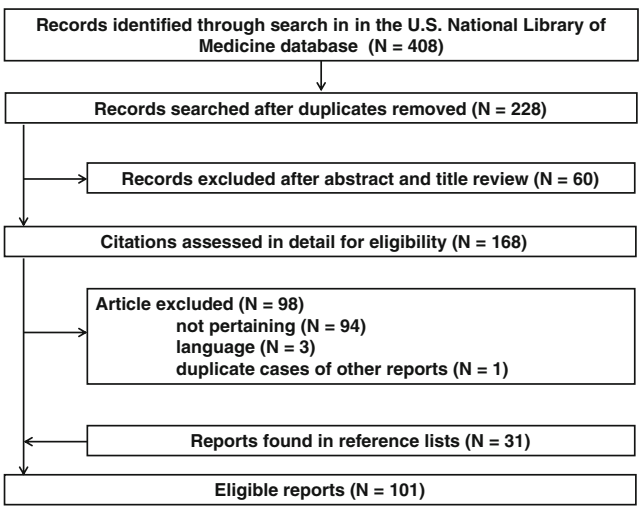

Fig. 1 Flowchart of the literature research process. Of the 101 reports included in the final analysis, 11 were identified exclusively from the Web-based Google research engine

Results

Presentation

In the 262 cystic fibrosis patients (male:female ratio 1.57; $P<0.01$) described in the 101 reports reviewed, hypochloremia (noted in 219/223 patients with this measurement), hyponatremia (in 206/218 patients), hyperbicarbonatemia (in 188/205 patients) or hypokalemia (in 161/199 patients) were found. Most cases of these electrolyte imbalances were in combination with some other condition, but less frequently they occurred in isolation (an electrolyte abnormality was detected in isolation when the other electrolytes went unmeasured), as shown in Table 1. Three-quarters of the patients were ≤2.5 years of age when diagnosed with electrolyte abnormalities, and approximately 60 % were diagnosed with electrolyte abnormalities before cystic fibrosis was identified (in at least 36 of these patients, a pediatric kidney disease specialist was involved because the initial diagnosis of Bartter syndrome was suspected). Circulating renin and aldosterone levels (Table 1), assessed only in a minority of cases, were almost always elevated (90 % and 86 %, respectively).

Clinical presentation was subacute in 172 cystic fibrosis patients (66 %) and chronic in the remaining 90 (34 %). Hyponatremia was significantly ($P<0.02$) more pronounced in patients with subacute rather than with chronic presentation (Table 1; Fig. 2). Renal function studies were performed only in a minority of subacute cases ($N=69$), with retention of urea and creatinine documented in 26 patients (38 %).

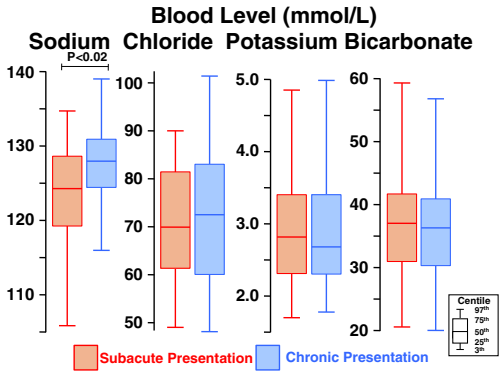

Fig. 2 Blood levels of sodium, chloride, potassium and bicarbonate in cystic fibrosis patients with electrolyte abnormalities. The results are given as "box and whiskers plot": *bottom and top of box* 25th and 75th centile, respectively, *middle of box* 50th centile (the median), *ends of whiskers* 3rd and 97th centile, respectively

In patients with either subacute or chronic presentation, these electrolyte abnormalities were associated with respiratory infections, excessive sweating, increased body temperature, failure to thrive, vomiting, heat exposure and fluid volume depletion, but they were significantly more frequent in patients with subacute presentation (Table 2). Tendency to recur was found in both subacute and chronic presentations, but was significantly ($P<0.02$) more common in subacute cases. Respiratory disease was significantly more pronounced in patients with electrolyte abnormalities than in those without these abnormalities in both subacute and in chronic cases [70, 94]. All reported patients had normal or low blood

Table 1 Laboratory values in cystic fibrosis patients with a tendency to hyponatremia (≤134 mmol/L), hypokalemia (≤3.4 mmol/L), hypochloremia (≤100 mmol/L) or hyperbicarbonatemia (≥27 mmol/L)

Demographic and clinical data	All		Subacute presentation		Chronic presentation		Significance (subacute vs. chronic)
	N	Value	*N*	Value	*N*	Value	
Gender, males/females (*N*)	262	160/102[b]	172	109/63[b]	90	51/39[b]	NS
Age (years)	262	0.58 [0.33-2.5]	172	0.50 [0.33-2.5]	90	0.58 [0.40-2.4]	NS
Cystic fibrosis undiagnosed (*N*)	262	152	172	112	90	40	$P<0.005$
Kidney injury (*N*)	69	26	69	26	–	–	–
Circulating							
Sodium (mmol/L)	218	125 [120–129]	156	124 [119–129]	62	127 [122–131]	$P<0.02$
Potassium (mmol/L)	199	2.8 [2.3-3.4]	138	2.8 [2.4-3.4]	61	2.6 [2.1-3.2]	NS
Chloride (mmol/L)	223	71 [62–81]	146	71 [63–82]	77	70 [60–81]	NS
Bicarbonate (mmol/L)	205	37 [32–42]	123	38 [33–42]	82	36 [31–41]	NS
Renin[a], elevated	31	28	18	16	13	12	NS
Aldosterone, elevated	29	25	16	14	13	11	NS

NS, Not significant

Numerical data are presented as the median and interquartile range (IQR) in square brackets; categorical data as are presented as relative frequency, unless otherwise indicated

[a] Estimated by either assays of plasma renin activity or by direct renin assay

[b] $P<0.01$ (male vs. female)

pressure, except for an adolescent with a tendency to arterial hypertension [80]. Sodium, potassium and chloride urinary excretion were found to be reduced when measured before treatment for fluid and electrolyte repair was initiated.

An adolescent with cystic fibrosis who took part in a football practice on a summer morning developed rhabdomyolysis and was found to be dehydrated and hyponatremic [49].

Metabolic alkalosis may lead to compensatory hypoventilation and $C0_2$ retention. To address this, an Australian group evaluated the acid–base balance in cystic fibrosis patients with chronic hypercapnia or exacerbations of respiratory disease and in adult patients with hypercapnia due to an exacerbation of their chronic obstructive pulmonary disease. The results of that study showed that metabolic alkalosis contributes to hypercapnic respiratory failure in cystic fibrosis patients during exacerbation of the disease itself [44].

Prevalence of electrolyte abnormalities at diagnosis of cystic fibrosis

Our literature research revealed only four reports addressing the prevalence of electrolyte abnormalities when cystic fibrosis was diagnosed. Hyponatremia was observed at diagnosis in 19 of 20 (95 %) Brazilian patients [42], whereas hypokalemia, hyponatremia and hyperbicarbonatemia were found in ten of 110 (9 %) Jordanian patients [94], four of 13 (31 %) Peruvian patients [95] and five of 120 (4 %) Indian patients [48].

Causes and clinical signs of fluid volume depletion in cystic fibrosis

A few of the identified studies investigated the mechanisms responsible for extracellular fluid volume depletion and electrolyte abnormalities in cystic fibrosis [16, 21, 55, 57, 81]. The results were as follows:

1) These patients underestimated their fluid needs and experienced excessive dehydration during extended exposure to hot climates and during intense physical activity [16, 55].
2) In cystic fibrosis, sweat production, occurring under conditions such as heat exposure or sport performances, was associated with an increase in sodium concentration in the sweat by approximately 30 mmol/L [21].
3) In salt-depleted patients with cystic fibrosis, clinical signs of extracellular fluid depletion, such as pallor, prolonged capillary refill, abnormal skin turgor, absent tears, dry mucous membranes, sunken eyes and tachycardia, were clinically less evident than in control subjects [57].
4) Apparently well hydrated and clinically stable cystic fibrosis patients had a low urinary sodium excretion [81] with elevated levels of both circulating renin and aldosterone [57], thus suggesting the presence of a chronic condition of fluid volume depletion.

Syndrome of inappropriate antidiuresis

Three patients with advanced cystic fibrosis (2 men and 1 woman, aged 23, 25 and 28 years, respectively) and a pulmonary exacerbation presented with hyponatremia (lowest value from 114 to 123 mmol/L) and no clinical signs of extracellular fluid volume depletion. Their acid–base balance and potassium level were normal, blood urea level was rather low and sodium and chloride urinary excretion were rather high. Hence, the diagnosis of syndrome of inappropriate antidiuresis was entertained [25, 77, 84].

Prevention and management of dyselectrolytemia

The salt content of a normal diet and of both breast milk and infant formula may well be inadequate to meet general nutritional requirements of cystic fibrosis patients [24, 26]. It has therefore been recommended that infants with cystic fibrosis who are fed breast milk or milk formula should normally be provided a sodium chloride supplement of 3 mmol/kg body weight. This dosage should be increased to 5–6 mmol/kg of body weight under circumstances such as hot weather, arid climate, excessive house heating or sports activity [24, 26,

Table 2 Factors associated with hyponatremia, hypokalemia, hypochloremia or hyperbicarbonatemia in patients with cystic fibrosis

Factors associated with electrolyte imbalance	All patients (N=262)	Patients with subacute presentation (N=172)	Patients with chronic presentation (N=90)	Significance (subacute vs. chronic)
Dehydration	146	133	13	P<0.0001
Heat exposure	127	105	22	P<0.0001
Vomiting	94	79	15	P<0.0001
Failure to thrive	88	48	40	P<0.002
Increased body temperature	75	61	14	P<0.0001
Excessive sweating	48	45	3	P<0.0001
Chest infection	40	35	5	P<0.001
Tendency to recur	71	57	14	P<0.02

Data are presented as the number (N) of patients

54]. Nonetheless, the authors of one study reported that an infant with cystic fibrosis developed severe hypernatremia (177 mmol/L) as a result of a misunderstood excessive daily supplement with one heaped teaspoon of table salt throughout a 3-week period [22].

Subacute dehydration and electrolyte abnormalities were repaired through the parenteral route in all reported cases, except for three rather mild cases that were managed by administration of oral rehydration solutions [17, 91, 93].

Discussion

This analysis shows that electrolyte abnormalities in cystic fibrosis patients are almost always associated with fluid volume depletion and are often clinically inapparent. Metabolic alkalosis and hypokalemia mainly result from renal tubular bicarbonate reabsorption, hydrogen secretion and potassium excretion, all of which are crucially regulated by a chloride–bicarbonate exchanger located on the intercalated cells and maintained in the presence of a reduced renal function [108]. This laboratory constellation is currently termed chloride depletion hypokalemic alkalosis instead of volume contraction hypokalemic alkalosis [108], taking into account that chloride depletion is the most significant factor responsible for these electrolyte abnormalities (Fig. 3).

These electrolyte abnormalities mainly affect cystic fibrosis patients aged ≤2.5 years, involve males more frequently than females, tend to recur and are often recognized before cystic fibrosis is diagnosed. Patients with subacute presentation of electrolyte abnormalities and dehydration often have a recent history of heat exposure, vomiting, excessive sweating, increased body temperature and respiratory infection. By contrast, the medical history of patients with chronic presentation is inconspicuous and subtle.

Medical history, low sodium, potassium and chloride urinary excretion, frequent activation of the renin–aldosterone system and occasional occurrence of some transient kidney injury in patients with subacute presentation all support the association between electrolyte abnormalities and fluid volume depletion in cystic fibrosis patients [109]. These patients underestimate their fluid needs and experience dehydration during exposure to heat conditions and physical activity at a time when they have an enhanced sweat production. Furthermore, a persisting and subtle condition of fluid volume depletion is often present in clinically stable and apparently well-hydrated cystic fibrosis patients.

Our review of the literature revealed a few adults with advanced cystic fibrosis who experienced an isolated hyponatremia event without fluid volume depletion and who were diagnosed with a syndrome of inappropriate antidiuresis [109]. However, we did not identify any case of hyponatremia due to inappropriate antidiuresis in children, adolescents or adults without advanced lung disease.

There are four possible consequences of electrolyte abnormalities in cystic fibrosis. These are:

1) Persistent sodium chloride depletion may cause failure to thrive [110]: even though in this condition poor growth is mainly linked to both pancreatic and lung disease, we posit that failure to thrive might at times also be related to chronic electrolyte abnormalities.
2) The lung disease of cystic fibrosis primarily develops because thick mucus plugs predispose to respiratory infections [9]. With electrolyte abnormalities and fluid volume depletion present, it is tempting to speculate that in cystic fibrosis electrolyte abnormalities might further

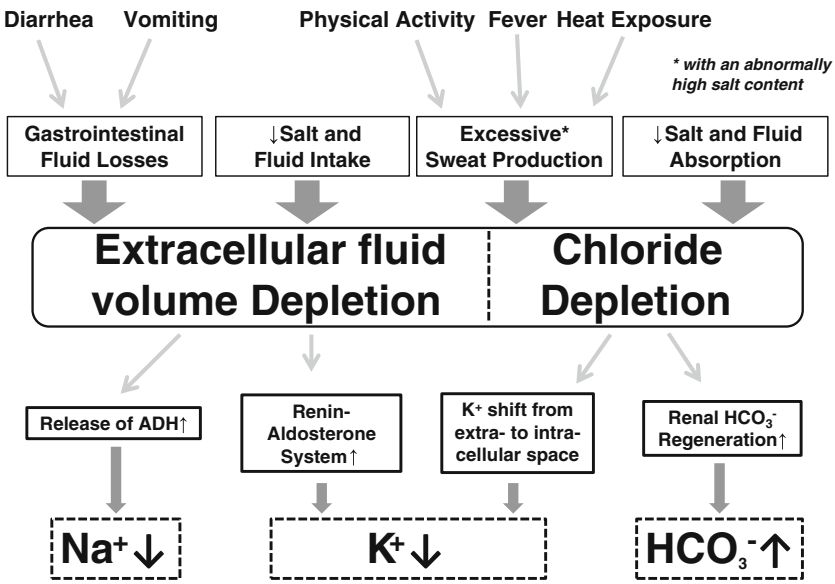

Fig. 3 Mechanisms underlying the development of electrolyte abnormalities in cystic fibrosis. The crucial role of a reduced renal function is not addressed in the figure. *ADH* Antidiuretic hormone

worsen the density and the viscosity of the mucus secretions.

3) In subjects with hyperbicarbonatemia, $C0_2$ retention develops in order to restore blood hydrogen ion concentration towards normal. Hence, in some cystic fibrosis patients, $C0_2$ retention might be linked not only to the lung disease but also to the hyperbicarbonatemia.
4) Adults with cystic fibrosis possess various potential risk factors for the development of chronic kidney disease, including cystic fibrosis-related diabetes mellitus, nephrotoxic drug exposure, secondary amyloidosis and absorptive hyperoxaluria. We speculate that in this hereditary disease recurrent but often clinically inapparent fluid volume depletion might be a further risk factor for chronic kidney disease.

In patients with subacute presentation, fluid volume depletion and electrolyte abnormalities require parenteral fluid and electrolyte replacement with solutions rich in sodium, potassium and chloride. Similar to the treatment for hypertrophic pyloric stenosis, many institutions give dehydrated cystic fibrosis patients with electrolyte abnormalities a 5 % glucose solution that contains sodium chloride at approximately 80 mmol/L and potassium chloride at 15–25 mmol/L [111]. Unfortunately, assessment of the fluid volume state of these patients based on physical examination and history is inaccurate. Yet, in cases with metabolic alkalosis, the severity of alkalosis may help clinicians estimate the fluid volume status and, therefore, the amount of fluid required for repair: 10 ml/kg of body weight of the above-mentioned solution reduces circulating bicarbonate by approximately 3 mmol/L [111]. Rather severe hyponatremic (<120 mmol/L) parenteral repair consists of a normal saline solution [108]. Most patients with chronic presentation require daily oral salt supplementation with 3 mmol/kg body weight. This dosage should be increased to 5–6 mmol/kg under particular circumstances such as hot weather, arid climate, excessive house heating or sport activities. When cystic fibrosis patients present with a severe form of chronic electrolyte abnormalities and dehydration, a period of extra-enteral (or parenteral) fluid and salt supplementation could be necessary.

A significant limitation of this review is that the analysis almost exclusively incorporated information from single case reports or small retrospective case series of cystic fibrosis patients. No attempt was made to objectively measure the body water compartments of the patients. Finally, therapeutic and preventive recommendations do not arise from scientific analysis or clinical outcomes, but from authors' opinions.

Conclusion

Cystic fibrosis itself tends to electrolyte abnormalities, such as hypochloremia, hyponatremia, hypokalemia or hyperbicarbonatemia, that are almost always associated with an often clinically inapparent fluid volume depletion. In such cases, kidney disease specialists are sometimes involved because the diagnosis of Bartter syndrome is initially suspected by general pediatric practitioners (the fractional chloride excretion, which is $>1.5\ 10^{-2}$ in Bartter syndrome and $<0.5\ 10^{-2}$ in cystic fibrosis and other conditions with strong renal salt retention, is a crucial diagnostic clue). While subacute presentation is treated parenterally, chronic presentation is managed with daily oral salt supplementation.

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