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Should Blood Gas Analysis Be Part of the Diagnostic Workup of Short Children? Auxological Data and Blood Gas Analysis in Children with Renal Tubular Acidosis

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Key Words
Renal tubular acidosis · Blood gas analysis · Growth monitoring

Abstract
Background: Renal tubular acidosis (RTA) is a rare cause of growth failure, therefore it is uncertain whether routine screening with blood gas analysis of short infants and children is cost-effective. ***Objective:*** To investigate the clinical, growth and laboratory parameters in children with RTA to estimate the possible value of laboratory screening for this disorder in infants and children referred for short stature according to a recent guideline. ***Method:*** Retrospective chart analysis of 30 children diagnosed between 1978 and 2005 in The Netherlands and 3 centers in Belgium. ***Results:*** The current guideline for short stature detected 33% of children with RTA. Assuming a pre-test probability of RTA of 0.6 per 100,000 births, the likelihood ratio of poor growth was 58 and 17 below and above 3 years, respectively. Sensitivity was 17/30 and 12/24 for a –2.0 SDS cutoff for weight and body mass index, respectively. In infants and toddlers diagnosed before 3 years of age, the mean weight loss was 1.5 SD, and 0.8 SDS in older children. In short children >3 years RTA was extremely rare, always associated with clinical symptoms, and rarely detected by blood gas analysis. ***Conclusion:*** According to our data a decreasing weight SDS for age is a sufficient indication to perform blood gas analysis in children <3 years of age, particularly in the presence of additional clinical features, whereas it can be omitted in short children >3 years of age.

Introduction

For early diagnosis of medical conditions that lead to growth failure, regular monitoring of growth in terms of length (between 0 and 2 years) or height (from 2 years onward) and weight is needed, as well as an evidence-based guideline on referral criteria. After referral, a thorough medical history and physical examination followed by screening laboratory tests are essential to detect disorders that may present without clinical symptoms and signs.

We have recently proposed auxological referral criteria with a good sensitivity (beyond the age of 3 years) to detect Turner syndrome and various other growth disor-

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ders at a specificity of approximately 99% [1]. We have also tested this guideline for its effectiveness in detecting celiac disease and cystic fibrosis, which showed that the change in body mass index is a better marker to detect both conditions, although the sensitivity is still low (approximately 30%) [2, 3].

Among children referred for failure to thrive or impaired growth, renal tubular acidosis (RTA) is one of the diagnostic considerations. Failure to thrive and/or growth retardation are often observed in this disease [4–6], thus one might consider testing for RTA through blood gas analysis (acid-base equilibrium). In fact, a blood gas analysis was included in the Dutch consensus-based guideline [7]. However, RTA is a rare condition, and in a retrospective analysis of 742 short children no case with RTA was found (although the compliance with the guideline was far from optimal) [8]. Among pediatric endocrinologists there is no worldwide consensus about including this test in the screening procedure for growth failure: only 32% of the participating pediatric endocrinologists considered blood gas analysis important in the evaluation of a child with failure to thrive [9].

In an effort to establish whether a blood gas analysis is indicated in the workup of growth failure, including failure to thrive, we investigated growth in patients diagnosed with RTA and compared this with the auxological referral criteria for growth failure.

Patients and Methods

We performed a retrospective chart analysis of all known Dutch patients and patients from 3 Belgian centers in whom the diagnosis of RTA had been made between 1978 and 2005. We estimated the number of births per year in this area at 200,000 per year, based on birth statistics in The Netherlands and Flanders. For this analysis growth data before and at diagnosis were analyzed. Length and height data were transformed to standard deviation scores (SDS; HSDS) [10]. Target height (TH) was calculated according to the Tanner formula (midparental height ±6.5) with an additional correction for secular trend (4.5 cm/generation) and expressed as SDS: (TH – 184)/7.1 for males and (TH – 170.6)/6.5 for females [10]. The length and height data of each patient were compared with the auxological criteria of the new guideline [1]. Weight data were collected and transformed to SDS (WSDS). Where appropriate the change in WSDS from its maximal value until WSDS at diagnosis was calculated. Body mass index (BMI) was calculated by weight/height squared and also expressed as SDS [11]. Finally, selected laboratory data at diagnosis were studied. RTA was diagnosed based on established criteria, including a low pH (<7.35), a low plasma bicarbonate (<21 mmol/l), elevated serum chloride (>106), and/or urine pH >5.3.

Table 1. Characteristics of RTA patients at diagnosis: auxology

Parameter at diagnosis	n	Median (range)	Mean ± SD
Age, years	30	0.5 (0 to16.6)	
HSDS	30	–2.0 (–5.5 to 1.3)	
HSDS – THSDS	18		–1.2 ± 1.8
WSDS	30		–2.3 ± 1.7
BMI SDS	24		–2.2 ± 1.7

SDS = Standard deviation score; HSDS = height or length SDS; THSDS = target height SDS; WSDS = weight SDS; BMI = body mass index.

Table 2. Characteristics of RTA patients at diagnosis: biochemical data

Patient No.	Age at diagnosis years	Sex	RTA type	pH blood	Bicarb. blood mmol/l	pH urine	Cl-blood mEq/l
1	0.01	M	ND	7.35	13.4	NA	111
2	0.01	M	D	7.33	17.0	9.00	NA
3	0.02	M	ND	NA	17.4	5.00	113
4	0.07	M	D	7.21	12.7	7.08	109
5	0.07	F	D	7.26	17.0	8.00	106
6	0.07	F	D	7.14	12.2	7.55	111
7	0.08	F	D	7.43	23.5	8.30	104
8	0.19	F	D	NA	14.6	7.00	108
9	0.21	F	D	7.22	11.0	7.00	145
10	0.24	M	D	7.39	9.0	7.70	124
11	0.33	M	D	7.22	14.9	8.00	NA
12	0.37	M	D	7.27	9.4	NA	108
13	0.40	F	D	7.40	15.9	7.00	110
14	0.43	M	D	7.34	14.2	6.00	112
15	0.47	F	D	7.37	22.0	7.00	115
16	0.51	F	D	7.38	19.5	6.00	111
17	0.58	F	ND	7.30	16.3	7.40	112
18	1.12	M	D	7.26	9.3	5.00	104
19	1.21	F	D	7.41	19.0	6.50	106
20	1.37	M	D	7.39	20.0	7.00	108
21	1.56	M	D	7.27	16.0	7.40	113
22	1.57	F	D	7.37	17.0	8.50	107
23	1.79	F	D	7.39	18.1	9.00	117
24	3.09	F	D	7.44	20.0	7.00	100
25	4.54	M	D	7.39	23.3	8.00	110
26	5.41	F	P	7.42	22.8	5.10	102
27	7.63	M	incomplete D	7.38	23.2	6.20	107
28	9.33	F	D	7.41	22.4	5.90	113
29	14.58	F	D	7.40	25.9	6.70	103
30	16.64	F	D	7.37	20.3	8.00	104

D = Distal; P = proximal; ND = type not defined; Cl = serum chloride; NA = not available.

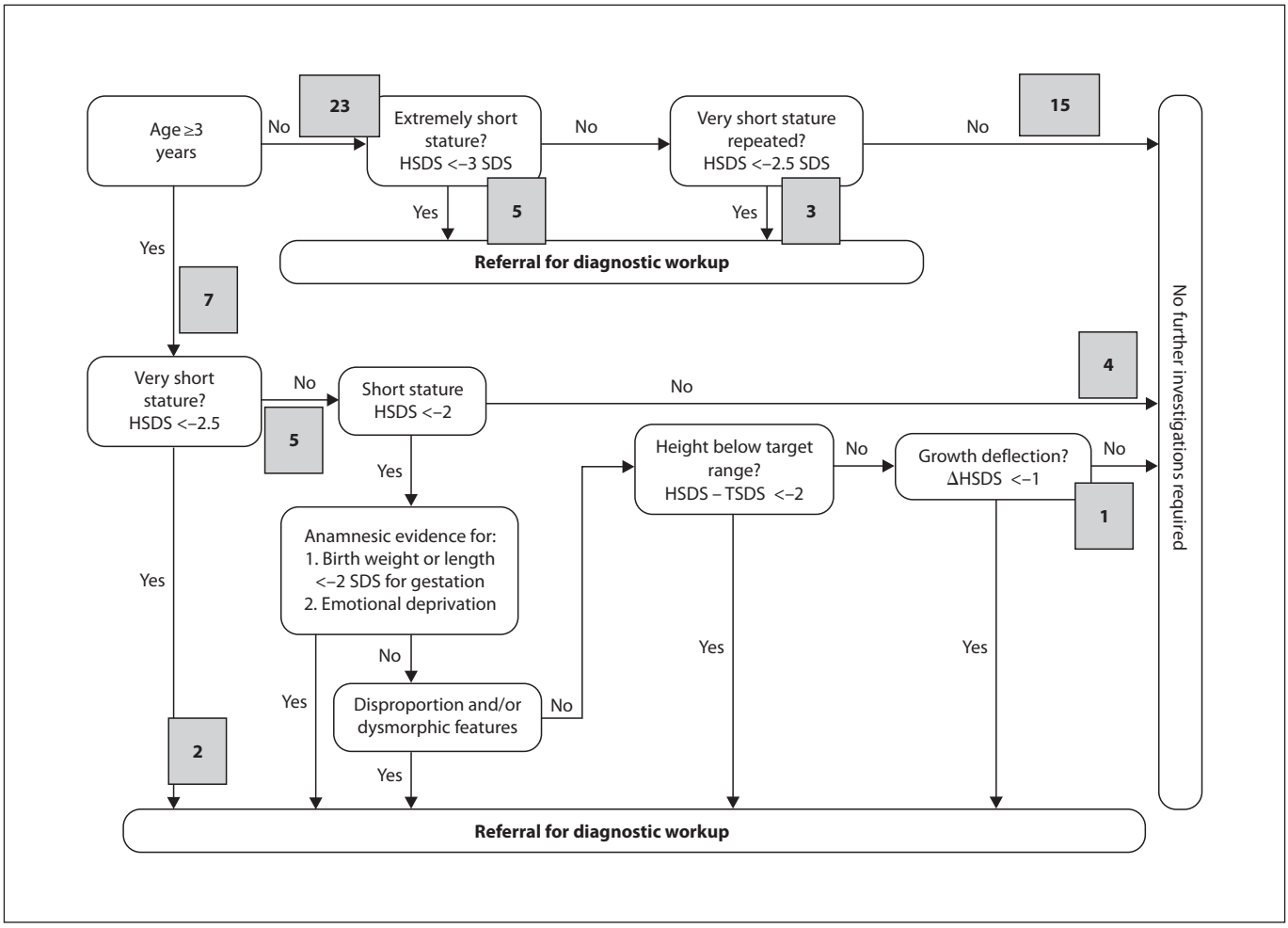

Fig. 1. The number of patients whose growth characteristics complied with the guideline for referral of short children. Growth data from patients with RTA were compared with the evidence-based guideline [1]. The numbers of patients < and ≥3 years of age from this study are given in gray squares.

Results

General Characteristics

Data of 33 patients (14 males) were obtained, but in 3 patients the data were incomplete and unsuitable for answering the study questions. Therefore, we used the data of 30 patients (13 males). A summary of the patient data is provided in tables 1 and 2. RTA was diagnosed before the age of 3 years in 23 children. Twenty-six patients had distal RTA, 1 proximal, and 3 were undefined. In 19 patients, blood pH was not <7.35. In these children, 12 had low bicarbonate levels according to the definition, 6 had urine pH >5.3, and in the final patient urine pH was just below 5.3, whereas the NH_4 excretion was abnormal in a specific test.

Comparison with the Referral Guideline for Length or Height

For each patient growth was compared with the decision rules from the new referral guideline, in order to assess whether the children with RTA would have come under medical attention when only their growth pattern was taken into account.

For infants and toddlers <3 years of age the referral criteria (HSDS <–3 SDS or repeatedly below –2.5 SDS) are very strict to prevent too many false-positives. Of the 23 children diagnosed before 3 years of age, 5 had a HSDS <–3 and 3 a HSDS repeatedly <–2.5. The growth patterns of the remaining 15 children did not fulfill the referral criteria (fig. 1). If a HSDS of <–2 was as a criterion, 11 of 23 children would be referred.

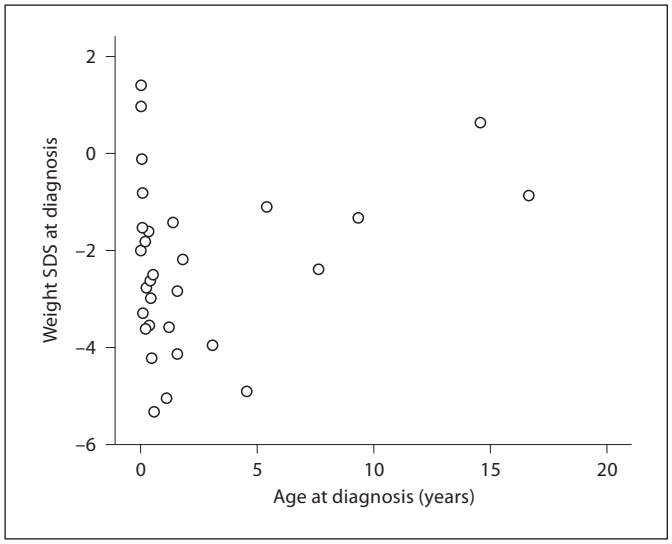

Fig. 2. Scatterplot of weight SDS versus age at diagnosis in 30 children; r = 0.26 (NS).

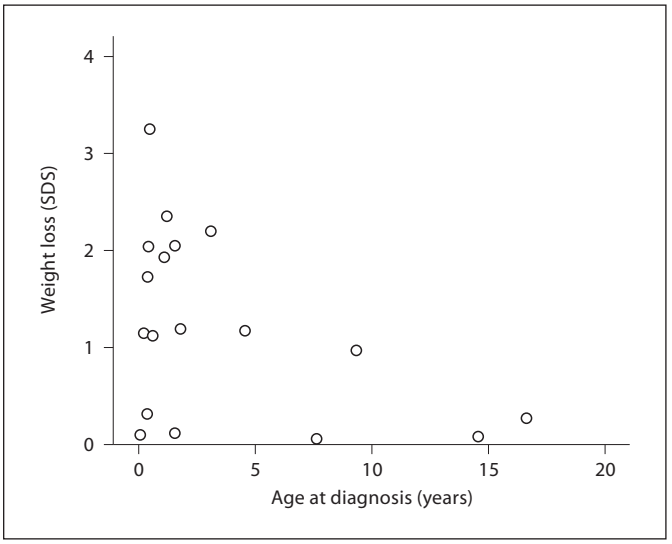

Fig. 3. Scatterplot of weight loss in the period previous to diagnosis versus age at diagnosis (n = 18, r = –0.47, $p < 0.05$).

Of the 7 children diagnosed ≥3 years of age, only 2 had a height SDS of <–2.5 and would therefore be referred. One patient had a HSDS between –2.5 and –2, but did not show height below the TH range or a growth deflection. The remaining 4 children had a HSDS of >–2.0 (fig. 1). Thus, the sensitivity of the referral criteria to detect RTA is only (8 + 2)/30 = 33%.

If one would assume that we have been able to collect all RTA patients born in a period of 28 years, the pretest probability of RTA can be estimated at 33 per 5,600,000 = 5.9 per 100,000 births. The 2×2 contingency table for the new auxological guideline in children <3 years is shown in table 3. The positive predictive value is 3 per 10,000, and the likelihood ratio for a positive result (LR+) is 58 (95% CI 33–102). For children ≥3 years, where both the sensitivity (2/7 = 29%) and specificity (98.3) are lower [1], the LR+ is 17 (95% CI 5–54).

Weight for Age and BMI

In patients diagnosed before 3 years of age, 14 of 23 had a WSDS of <–2 at diagnosis, and in older patients 3 of 7 (total 17/30). Only 2 patients had a weight of >0 SDS. In children <3 years, mean weight loss in the period prior to diagnosis, expressed as the difference between maximal WSDS and WSDS at diagnosis, was 1.5 SDS (SD 1.0, n = 12), and in the older age group median weight loss was 0.8 SDS (range 0.1–2.2, n = 6). Overall, the median weight loss was 1.2 (range 0.1–3.3, n = 18; in some patients diagnosed shortly after birth no reliable loss in weight could be calculated). The correlation between age at diagnosis and WSDS at diagnosis was 0.26 (NS), while the correlation between age at diagnosis and weight loss was –0.47 ($p < 0.05$; n = 18; fig. 2, 3). This suggests that weight loss might be an additional parameter in infants and toddlers

Table 3. 2×2 contingency table showing estimates of positive and negative test results for RTA if the guideline for referral of growth failure were to be used for children <3 years

Test	RTA	No disease	Total
Positive	8	23,418	23,426
Negative	15	3,879,589	3,879,604
Total	23	3,903,007	3,903,030

Sensitivity = 8/23 = 0.35.

Number of false-positives = 0.06 × 3,903,007 = 23,418.

Prevalence of disease (diagnosed at <3 years; pretest probability) = 23/3,903,030 = 0.59/100,000.

Positive predictive value = 8/23,418 = 0.00034 (3.4 per 10,000, 95% CI 1–6 per 10,000).

Likelihood ratio for a positive result (LR+) = se/(1 – sp) = 58 (95% CI 33–102).

Likelihood ratio for a negative result (LR–) = (1 – se)/sp = 0.66 (95% CI 0.49–0.88).

The total number of children born in 28 years corrected for the RTA patients who were diagnosed before 3 years of age was estimated at 23/33 × 5,600,000 = 3,903,030. The specificity of the guideline is 99.4% [1].

for the diagnosis of RTA. However, the numbers of patients are small, and the difference between both age groups did not reach statistical significance.

In 6 children BMI could not be calculated due to young age (<2 months) at diagnosis. In the other 24 children mean BMI SDS at diagnosis was –2.2 (range –5.9 to +1.0 SDS, SD 1.7). In patients diagnosed before 3 years of age, 10 of 17 had a BMI SDS of <–2, and in older patients 2 of 7. The difference in BMI SDS at diagnosis between the youngest and older age group did not reach statistical significance, although the younger children tended to have lower BMI SDS. The number of children who complied with the decision rule that proved most effective for celiac disease and cystic fibrosis (combining BMI SDS of <–2 and change in BMI of >0.5/year) [2, 3] was 7/9.

Combination of Auxological Parameters

If one single auxological criterion was chosen, in children <3 years a WSDS of <–2 would yield the highest sensitivity (14/23, 61%), and sensitivity would increase to 15/23 (65%) if HSDS or WSDS were <–2. In older children a height SDS of <–2 would result in a sensitivity of 3/7 (43%), and this would increase to 4/7 (57%) if HSDS or BMI SDS were <–2. A similar result would be obtained if WSDS or BMI SDS were <–2.

Clinical Presentation and Blood Gas Analysis

There are two additional factors that have to be taken into account before the decision is made to perform blood gas analysis in infants and children with failure to thrive or other forms of growth failure: (1) how often growth failure was the only presenting symptom, and (2) the diagnostic value of blood gas analysis.

In children <3 years, 4 of 23 had a blank medical history besides failure to thrive or another form of growth failure. Other reasons for referral were a positive family history for RTA, renal stones, recurrent urinary tract infections, constipation or vomiting. In the 7 children diagnosed at 3 years of age or older, none was symptom-free at diagnosis. Symptoms included bowing of the legs, tiredness, recurrent infections of the urinary tract and renal stones.

As shown in table 2, the diagnostic value of blood gas analysis is reasonable in infants (only 2 of 23 cases had an initial normal result, defined as pH >7.35 and a bicarbonate >21). However, in older children, only in 2 of 7 was bicarbonate slightly decreased and pH was always >7.35. Thus, blood gas analysis has a low diagnostic validity in that age group.

Discussion

We have shown that in children <3 years of age the referral guideline, based on length data alone, has a positive likelihood ratio of 58, suggesting that the guideline is a useful tool for screening of children with RTA. However, the sensitivity to detect children with RTA is low, as a considerable percentage of children (15/23) would not have been diagnosed by monitoring growth alone according to the guidelines. Weight and weight loss appear better markers. However, most infants present not only with growth failure, but also with one of the other signs or symptoms associated with RTA. Blood gas analysis was abnormal in 21/23 cases. In contrast, in children older than 3 years the prevalence of RTA is considerably lower, the percentage of children with poor growth detected by applying the guideline is lower (2 of 7), all children had additional signs and symptoms, and the diagnostic value of the blood gas analysis was low. This means that screening all asymptomatic short children of >3 years using blood gas analysis would not be cost-effective.

Among the many causes of failure to thrive or impaired growth, renal disease is an important category to consider. On the one hand, chronic renal insufficiency may lead to impaired growth [12], but chronic states of acidosis, as in RTA, are also known to induce growth retardation [4, 13]. Acidosis in RTA may be caused by: (1) tubular failure to secrete hydrogen ions by the distal convoluted tubule; (2) urinary bicarbonate wasting due to proximal convoluted failure, or (3) a mixed mechanism. The diagnosis and classification of RTA have traditionally been based on functional studies. In the last decade, application of molecular biology techniques has opened a new perspective to the understanding of the pathophysiology of inherited causes of RTA. Gene mutations have been identified in RTA combined with ocular abnormalities and sensorineural deafness (SLC4A4 and ATP6B, respectively) [14]. However, in the human, none of these genes was linked to disturbances in the growth axis.

The mechanism of failure to thrive in RTA is not completely understood. In the older literature it was observed that treatment of the acidosis per se led to improvement of growth, suggesting an inhibitory effect of acidosis on growth [15]. In contrast, Glaser et al. [16] suggested a role for growth hormone in maintaining normal acid-base homeostasis, and thus growth hormone deficiency should be considered in cases of acidosis and growth failure. Based on literature from the 1970s, Tsuru and Chan [17] suggested that growth failure in acidosis is probably related to disturbances in vitamin D and calcium metabo-

lism. This was not in accordance with later studies as summarized by Donckerwolcke et al. [4] who also discussed the inconsistent findings on either impaired or normal growth hormone secretion during acidosis. More recently, Mitch [18] summarized the metabolic and clinical consequences of metabolic acidosis. He concluded that abnormalities in the GH-IGF axis occur due to acidosis (e.g. blunted IGF-1 response to GH). However, some data are derived from animal studies and contrast with human adult data, so that the applicability to the situation in children is uncertain.

In order to trace children with RTA as early as possible, the clinician should be alert to failure to thrive and other RTA symptoms (nausea, vomiting, weight loss, a positive family history, nephrocalcinosis, renal stones, rickets and bone demineralization), and be aware that the guideline for growth monitoring only detects a small percentage of cases. We obtained similar findings in two other diseases that can be detected at an early age by failure to thrive: celiac disease and cystic fibrosis [2, 3]. In studies on the best decision rules that could be applied to detect these conditions, we showed that the overall performance of detecting both disorders with statural growth parameters is moderate, and that in the first year of life weight is a better auxological tool for detection than length [2, 3]. Furthermore, the deflection of weight and BMI is more important than weight or BMI SDS per se.

Concerning weight, we observed that a decrease in WSDS in the period prior to diagnosis is more marked in the younger age group. Apparently, weight loss is a stronger marker of disease in young infants. Using the decrease in weight as a criterion for referral, a decrease in weight of 1.5 SDS would lead to referral of more than 50% of RTA patients, but only in the group <3 years. Weight loss seems to play a lesser role in the clinical course of older children. The combination of several auxological criteria had no additional value when compared with the use of only 1 parameter. Weight appeared to be a more sensitive predictor of RTA than length.

A limitation of this study is the small number of patients, incomplete data, and the retrospective design. Although we presume that we included all patients in The Netherlands and in 3 Belgian centers, possibly several older children with a mild phenotype may not have been included in the study. Still, it will be difficult to collect a larger dataset, and we believe that our results are representative for RTA patients in other geographic areas. A second limitation is that the rarity of the disease leads to a very low probability before any clue from the medical history, growth and physical examination is taken into account. However, most patients did have some symptoms, which increases the pretest probability. Furthermore, the pretest probability would be much higher in patients with a family history of RTA than for those with nonspecific symptoms. A third limitation is that there is admittedly some degree of subjectivity in the interpretations of the various likelihood ratios, and therefore it remains uncertain how these data can be translated to cost-effectiveness.

In conclusion, the proposed auxological guideline only detects one third of children with RTA. A cutoff for weight or BMI SDS has a better sensitivity, similar to our previous findings in celiac disease and cystic fibrosis. In children <3 years a decreasing weight for age is a sufficient indication to perform blood gas analysis, particularly in the presence of additional clinical features. This laboratory measure can be omitted in asymptomatic short children ≥3 years, because of the extremely low prevalence of RTA in that age group, and the low sensitivity of growth failure and blood gas analysis.

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