Published online: 2019-04-25

Low Plasma Sodium Concentration Predicts Perforated Acute Appendicitis in Children: A Prospective Diagnostic Accuracy Study

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Eur J Pediatr Surg 2020;30:350–356.

Abstract

Introduction Early differentiation between perforated and nonperforated acute appendicitis (AA) in children is of major benefit for the selection of proper treatment. Based on pilot study data, we hypothesized that plasma sodium concentration at hospital admission is a diagnostic marker for perforation in children with AA.

Materials and Methods This was a prospective diagnostic accuracy study, including previously healthy children, 1 to 14 years of age, with AA. Blood sampling included plasma sodium concentration, plasma glucose, base excess, white blood cell count, plasma arginine vasopressin (AVP), and C-reactive protein.

Results Eighty children with histopathologically confirmed AA were included in the study. Median plasma sodium concentration on admission in patients with perforated AA (134 mmol/L, [interquartile range 132–136]) was significantly lower than in children with nonperforated AA (139 mmol/L, [137–140]). The receiver operating characteristic curve of plasma sodium concentration identifying patients with perforated AA showed an area under the curve of 0.93 (95% confidence interval, 0.87–0.99),

Keywords
- acute appendicitis
- appendectomy
- pediatric surgery
- plasma sodium concentration
- diagnostic accuracy

received
December 21, 2018
accepted after revision
March 9, 2019
published online
April 25, 2019

DOI https://doi.org/10.1055/s-0039-1687870.
ISSN 0939-7248.

with a sensitivity and specificity of 0.82 (0.70–0.90) and 0.87 (0.60–0.98), respectively. Plasma sodium concentrations $\leq$136 mmol/L resulted in an odds ratio of 31.9 (6.3–161.9) for perforation. The association between low plasma sodium concentration and perforated AA was confirmed in a multivariate logistic regression analysis. Median plasma AVP on admission was higher in patients with perforated (8.6 pg/mL [5.0–14.6]) as compared with nonperforated AA (3.4 pg/mL [2.5–6.6]).

Conclusion In children with AA, there is a strong association between low plasma sodium concentration and perforation, a novel and not previously described finding.

Introduction

Acute appendicitis (AA) is a common surgical emergency in children, and acute appendectomy is the most common emergency operation on this population. The diagnostic method to differentiate AA from other causes of abdominal pain has evolved over the years. Initially AA was a clinical diagnosis, later aided by biochemical markers showing signs of inflammation. In 1985, Gale et al presented computed tomography (CT) as a diagnostic tool for AA,[1] followed by Puylaert's description of ultrasound diagnosis[2] in 1986 and Incesu et al's introduction of magnetic resonance imaging in 1997.[3] Simultaneously several clinical scores have been presented, giving the clinician support in making the diagnosis of AA or to differentiate between perforated and nonperforated AA.[4] Finally, novel biochemical markers have been tested with the ambition of increasing the accuracy of the diagnosis.[5,6]

At the same time, the treatment has changed from laparotomy on wide indications, via minimally invasive procedures to recent advances in nonoperative treatment of AA.

The historical dogma that AA always progresses to gangrene and perforation was challenged[7] and has now been rejected.[8] Hence, there may be an increasing benefit in the ability of differentiating perforated from nonperforated AA in modern treatment algorithms.

Plasma sodium concentration at admission to the pediatric emergency department was chosen as a marker to differentiate between perforated and nonperforated AA. The reason to test plasma sodium concentration originates from an earlier postoperative study, where only patients with perforated AA were planned for inclusion.[9] One of the inclusion criteria was normonatremia at the end of surgery. The study could not be conducted due to a very high prevalence of hyponatremia. Based on these pilot data, we hypothesized that plasma sodium concentration might act as a marker to differentiate between perforated and nonperforated AA. Arginine vasopressin (AVP) concentration is often increased in inflammatory states such as acute pediatric surgery.[10] To investigate a possible mechanism of hyponatremia development, AVP was also measured on admission.

The primary objectives of this study were to investigate the association between plasma sodium concentration on hospital admission and perforation status in children with AA and to evaluate the characteristics of plasma sodium concentration on admission as a clinical marker for perforation status in children with AA.

Materials and Methods

Study Design and Participants

This prospective diagnostic accuracy study was conducted at the Department of Pediatric Surgery at Astrid Lindgren Children's Hospital, Karolinska University Hospital in Stockholm, Sweden, a tertiary referral center for Pediatric surgery. Patients were included between May 2016 and July 2017, with an interruption for 3 months during the relocation to a new hospital building, providing a total inclusion time of 10 months. The intended study population and the final inclusion criteria were previously healthy children, 1 to 14 years of age, with a histopathologic diagnosis of AA according to Carr.[11] Histopathologic perforation was defined as a macroscopic or microscopic perforation with loss of appendix wall integrity.

Previously known metabolic or endocrine diseases were exclusion criteria. The study protocol was approved by the Regional Ethics Review Board in Stockholm (reference No. 2016/181–31/2). The study protocol was registered at the Australian New Zealand Clinical Trial Registry (ACTRN 12617000047392).

Procedures

Children presenting at the pediatric emergency department with symptoms of suspected appendicitis were invited to participate, and their parents were presented formalized oral and written study information. All patients underwent imaging diagnostics, in 78 cases ultrasound and in 2 cases CT, which depending on clinical status was performed before or after inclusion. For study participants, written consent was obtained prior to inclusion and blood sampling, which was performed before any intravenous rehydration and/or drug treatment was given. Children who were eventually not diagnosed with AA were not included in the study.

Blood sampling for the study included bedside blood gas analysis (ABL 90 Flex Plus [ABL], Radiometer Medical ApS, Denmark) where plasma sodium concentration, plasma glucose (P-glucose), and base excess (BE) were obtained. The latter two variables were included since they theoretically may show an association with perforated appendicitis due to possible increased insulin resistance and starvation, respectively, in these patients. In addition, white blood cell count (WBC) and C-reactive protein (CRP) were determined as part of routine testing in this patient group. These variables were analyzed at the Karolinska University Hospital Laboratory according to standard procedures. Plasma-AVP

was obtained in 52 patients (10 patients with and 42 without perforated appendicitis) and was determined by radioimmunoassay as previously described,[12] using a specific AVP antibody (AB3096).[13] AVP was extracted from plasma using Sep-Pak Plus C18 extraction cartridges (Waters Corporation, Milford, Massachusetts, United States). The detection limit was 0.10 pg/mL plasma and the interassay coefficient of variation was 8%.

The sodium concentration analysis was based on potentiometric measuring principles in plasma. The variation in plasma sodium concentration has been investigated with a resulting coefficient of variation of 0.2 to 0.3% using this method.[14]

Patient age (years) and sex, symptom duration (days), and body temperature (°C) were registered at admission to the pediatric emergency department.

Statistical Analysis

Pilot observations suggested that a difference of 3 mmol/L in plasma sodium concentration and a standard deviation 2 mmol/L was applicable to the present study in similar patients, corresponding to a standardized effect size of 1.5 (effect size = difference/standard deviation). Retrospective data suggested a rate of perforated appendicitis of ~20% among acute appendectomies at our hospital. With a total study size of $n = 80$ and at least 10 of these in the perforated group, there is a power of 80% to find a standardized effect size of 1.0 with a two-sided *t*-test and a significance level of 5%, corresponding to a difference of equal size as the standard deviation.

D'Agostino & Pearson omnibus normality test was used to assess normality. Normally distributed data are presented as mean (95% confidence interval [CI]) and nonparametric data are presented as median (interquartile range [IQR]).

Student's *t*-test or Wilcoxon matched pair test was used as applicable, Mann–Whitney U-test was used to compare groups with nonparametric data, and two-sided Fisher's exact test was used to compare dichotomized variables. Receiver operating characteristic (ROC) curve analysis was performed to assess the best cutoff for the prediction of perforated AA and values for area under the curve (AUC), sensitivity, and specificity are given as mean (95% CI of the mean).

GraphPad Prism 6 was used for the statistical analyses (GraphPad Software, Inc. La Jolla, California, United States), except the power analysis that was performed by Dell Statistica 13.2 (Dell Software, Inc. Round Rock, Texas, United States).

Predictors of perforated AA were analyzed by univariate logistic regression followed by step-wise forward multiple logistic regression using the NCSS software (NCSS11, Kaysville, Utah, United States). The variables included in the univariate analysis were sodium concentration, glucose concentration, BE, symptom duration, CRP concentration, WBC, temperature, and age. Only factors with a univariate $p < 0.2$ were used in the multiple logistic regression analysis, and a decrease in deviance by 3.84 ($p = 0.05$) was necessary for an item to be included in the final predictive model.

The study was conducted according to the Standards for Reporting Diagnosis Accuracy Studies.[15]

Role of the Funding Source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the article.

Results

Included and excluded patients are presented in ►Fig. 1. During the active inclusion periods, 228 children with suspected AA were admitted to the pediatric emergency department; 212 children were diagnosed with AA and underwent subsequent laparoscopic appendectomy. Nine children were randomized to nonoperative treatment in a randomized controlled trial, the Appendectomy Versus Non-Operative Treatment For Acute Nonperforated Appendicitis in Children (APPY)-trial.[16] Another seven children accepted participation in the study and had blood samples taken on admission, but were later excluded, as they were not diagnosed with AA, nor had an appendectomy. Out of the 212 patients later having an appendectomy, seven declined participation in the study and 125 were never asked to participate. Eighty children with AA, that was later confirmed by histopathology, were included in the study and final analyses.

Patient characteristics of all eligible patients and the 80 children included in the study are presented in ►Table 1.

Age, sex, CRP, WBC, duration of symptoms, and proportion of perforated AA were comparable between included and not included patients.

On admission to the pediatric emergency department, the median plasma sodium concentration in patients with perforated AA was significantly lower as compared with patients with nonperforated AA, 134 (IQR 132–136) mmol/L and 139 (IQR 137–140) mmol/L, respectively (►Fig. 2). The patients who were sampled at the pediatric emergency department but later excluded as they did not have appendicitis ($n = 7$) had similar median plasma sodium concentration, 139 (IQR 138–141), as compared with patients with nonperforated AA.

The ROC curve of plasma sodium concentration at admission identifying patients with perforated AA showed an AUC of 0.93 (95% CI, 0.87–0.99). A cutoff value of plasma sodium

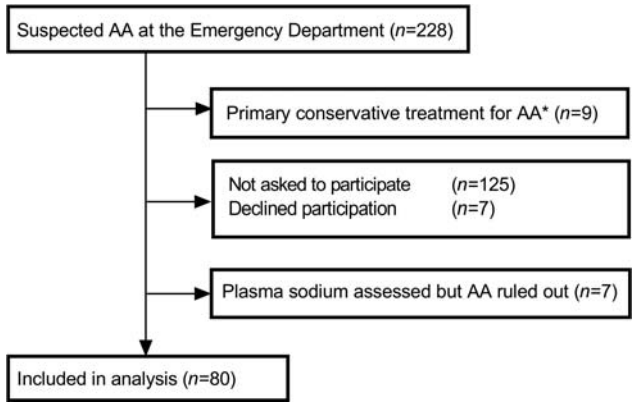

Fig. 1 STARD flow-chart. *Denotes patients that were randomized to not having appendectomy within the APPY trial.[16] AA, acute appendicitis.

Table 1 Patient characteristics on admission to the pediatric emergency department

	Included	Not included	*p*-Value	Perforated appendicitis	Nonperforated appendicitis	*p*–Value
	$n = 80$	$n = 132$		$n = 15$	$n = 65$	
Age (years)[a]	9.2 (7.3–11.1)	8.9 (6.6–11.2)	0.511	7.5 (6.3–9.5)	9.2 (8.0–11.1)	0.167
Male, *n* (%)	53 (66)	69 (52)	0.062	12 (80)	41 (63)	0.245
CRP (mg/L)	32 (13–66)	44 (16–88)	0.134	79 (44–119)	24 (9–54)	<0.001
WBC (x10^9/L)	14.1 (10.3–17.7)	14.9 (11.8–17.8)	0.353	17.1 (14.0–18.9)	13.5 (10.3–17.4)	0.026
Symptom duration (days)	2 (1–3)	2 (1–3)	0.057	3 (2–4)	2 (1–2.5)	<0.001
Perforation (%)	19	23	0.493	100	0	
Plasma sodium (mmol/L)[a]	138 (136–140)			134 (132–136)	139 (137–140)	<0.001
Body temperature (°C)	37.5 (37.1–38.0)	37.7 (37.2–38.2)	0.236	37.8 (37.4–38.8)	37.5(37.1–37.9)	0.052
Plasma glucose (mmol/L)	5.1 (4.7–5.9)			5.4 (4.9–7.3)	5.1 (4.7–5.8)	0.020
Base excess (mmol/L)	−0.4 (−2–0.5)			−2 (−5–1)	−0.2 (−1.6–0.6)	0.003
AVP (pg/mL) $n = 52$	4.2 (2.8–7.9)			8.6 (5–14.6) $n = 10$	3.4 (2.5–6.6) $n = 42$	0.004

Abbreviations: AVP, arginine vasopressin; CRP, C-reactive protein; WBC, white blood cell count.
Note: Data are expressed as mean (95% confidence interval).
[a]Data are expressed as median (interquartile range).

concentration of ≤136 mmol/L was shown to give the best possible sensitivity and specificity, 0.82 (95% CI, 0.70–0.90) and 0.87 (95% CI, 0.60–0.98), respectively ($p < 0.001$) (►Fig. 3). By Fisher's exact test on dichotomized data, plasma sodium concentration ≤136 mmol/L was associated with an odds ratio (OR) of 31.9 (95% CI, 6.3–161.9), or a 15-fold increase in relative risk (RR) (RR = 15, 95% CI, 3.7–62) for perforation compared with values >136 mmol/L, with similar sensitivity and specificity as compared with when continuous data was used (►Fig. 4).

Measures of possible and commonly used predictors of perforated AA are given in ►Table 2. From these univariate data, a forward stepwise multiple logistic regression analysis was performed. This analysis confirmed the association between low plasma sodium concentration and perforated AA. Starting with plasma sodium concentration as the strongest predictor, adding any of the other proposed factors failed to statistically improve the predictive model.

On admission, median plasma AVP concentration was higher in patients with perforated as compared with

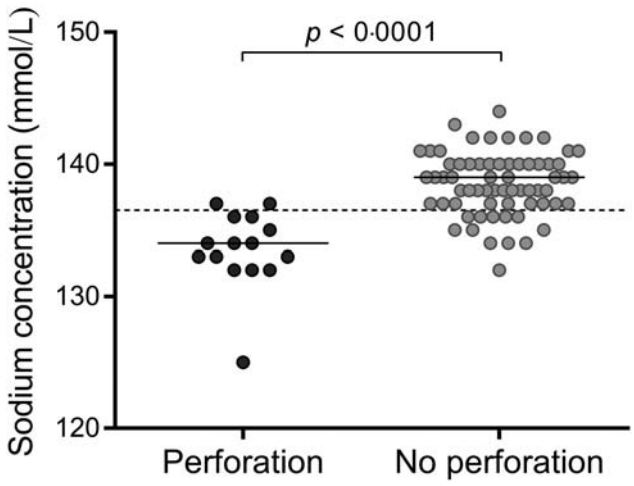

Fig. 2 Plasma sodium concentrations at admission to the emergency department were compared in patients with acute appendicitis verified by histopathology, with and without perforation, respectively. Lines denote median values, whereas dashed line corresponds to the chosen value for dichotomization of data. The *p*-value was obtained by Mann–Whitney *U*-test.

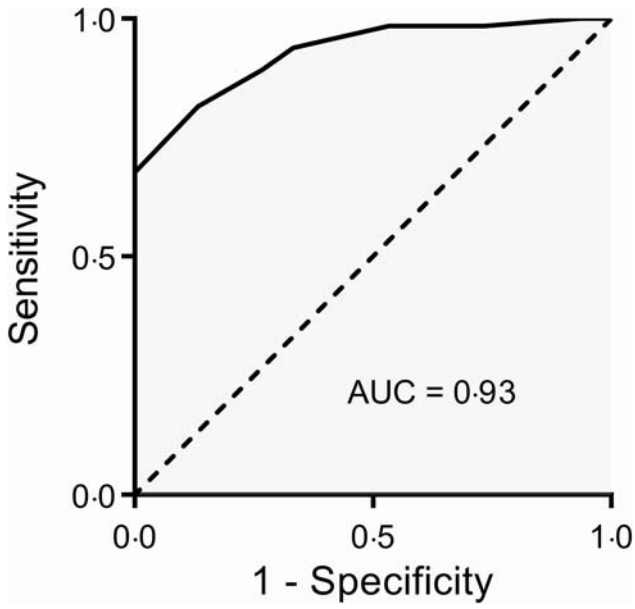

Fig. 3 Receiver operating characteristic curve for plasma sodium concentration as a predictor of perforated AA. AUC is area under the curve; dashed line is the line of no predictive value, that is, AUC = 0.5.

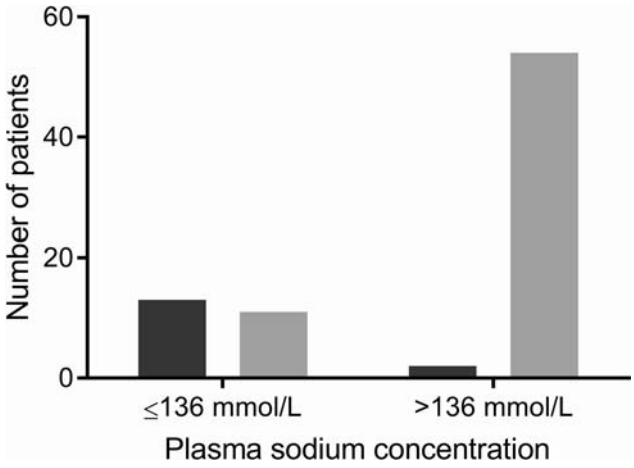

Fig. 4 Plasma sodium concentration dichotomized at ≤136 mmol/L and >136 mmol/L, respectively. Dark bars denote perforated AA, gray bars denote nonperforated AA. Odds ratio was 31.9 (95% CI, 6.3–161.9) by Fisher's exact test, sensitivity 0.87 (95% CI, 0.60–0.98), and specificity 0.83 (95% CI, 0.72–0.91). AA, acute appendicitis; CI, confidence interval.

nonperforated appendicitis, 8.6 (IQR, 5.0–14.6) and 3.4 (IQR, 2.5–6.6) pg/mL, respectively ($p = 0.004$) (►Table 1).

As a post-hoc analysis not included in the original protocol, the sensitivity and specificity for ultrasound imaging to predict perforation were calculated. Ultrasound imaging was performed in 78 of the patients and indicated perforation in 14 patients, whereof perforation was later confirmed histopathologically in six patients. Ultrasound ruled out perforation in 64 patients, whereof perforation was later confirmed in seven patients. Hence, the sensitivity and specificity for ultrasound in predicting perforation later confirmed or ruled out by histopathology were 0.46 and 0.88, respectively.

Discussion

The main finding of this prospective diagnostic accuracy study was a strong correlation between low plasma sodium concentration on hospital admission and perforation in children with AA. Children with perforated AA had significantly lower plasma sodium concentration as compared with children with nonperforated AA. In addition, low plasma sodium concentration had a high predictive value discriminating between perforated and nonperforated AA. In children with AA and plasma sodium concentration of ≤136 mmol/L at emergency department admission, there was a 32-fold increase in OR of finding a perforated AA. In the multivariate analysis, none of the commonly used variables predicting the severity of AA (CRP, WBC, temperature, duration of symptoms, and age) improved the prediction obtained from plasma sodium concentration alone. BE and P-glucose (included in the blood gas analyses) were also found to be associated with perforated AA, but the contribution to overall accuracy (plasma sodium concentration + BE + P-glucose) was minor as compared with plasma sodium concentration alone. However, with only 15 cases, multiple significant predictors are unlikely to be found in a multivariate analysis, and their absence must be interpreted with caution.

Possible limitations of the current study are inherent to the sample size and the single center study design. Further drawbacks are the interruption of the inclusion period and that the patients were not consecutively included. Nonetheless, the validity of the study is enhanced by the prospective design. Furthermore, our results remain to be reproduced in larger, prospective multicenter trials before being incorporated into standardized pathways for diagnosing AA in children.

The findings of this study are consistent with our pilot data observations and also with the sparse previous retrospective data on plasma sodium concentration as a marker in children[17] and adults[18,19] in this context. A recent meta-analysis found the pooled sensitivity and specificity to differentiate complicated (perforated or gangrenous appendicitis) from noncomplicated AA to be within the range of 0.14 to 0.59 and 0.74 to 1, respectively, when nine different CT features informative for complicated AA were studied.[20] Compared with this, our findings with sensitivity and specificity of 0.82 and 0.87, respectively (►Fig. 4) combined with a ROC curve AUC of 0.93 are notable. The post-hoc finding of a

Table 2 Predictors of perforated appendicitis by univariate logistic regression ($n = 80$)

Variable	OR (95% CI)	*p*-Value	Correctly classified (%)
Sodium (per mmol/L)	2.3 (1.5–3.4)	< 0.001	81.1
Sodium (dichotomized)[a]	25.5 (5.0–128.0)	< 0.001	81.1
Glucose (per mmol/L)	1.6 (1.0–2.6)	0.032	63.5
Base excess (per mmol/L)	1.6 (1.2–2.1)	<0.001	71.6
Symptom duration (days)[b]	0.73 (0.54–0.99)	0.041	75.7
CRP (per mmol/L)	0.98 (0.97–0.99)	0.009	78.4
WBC (per 10^9/L)	0.87 (0.78–0.96)	0.005	71.6
Temperature (per C°)	0.51 (0.23–1.12)	0.054	66.2
Age (per year)	1.2 (0.93–1.49)	0.159	62.2

Abbreviations: CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; WBC, white blood cell count.
Note: The investigated predictors are treated as continuous parameters.
[a]Cutoff at ≤136 mmol/L.
[b]Per 1 day increase.

sensitivity and specificity of ultrasound to predict perforation of 0.46 and 0.88, respectively, also indicates that this imaging modality would benefit from other indices of perforation such as plasma sodium concentration, in our setting.

Differentiation between uncomplicated and complicated appendicitis is not possible before treatment as there is no proper modality to differentiate between phlegmonous and gangrenous appendicitis except histopathology. Multiple randomized controlled trials, both presented[21] and ongoing, use suspected perforated appendicitis as an exclusion criterion. For these reasons, the differentiation of perforated appendicitis will become increasingly important as differentiated treatment modalities are developed for the subtypes of nonperforated and perforated AA. There is evolving evidence that medical treatment of nonperforated AA is safe, feasible, and noninferior to appendectomy, in both children and adults.[21–23] Children with abdominal comorbidity such as previous abdominal surgery or children with respiratory compromise such as ongoing infections or cystic fibrosis may benefit the most from nonoperative treatment of nonperforated AA. Whether determination of plasma sodium concentration will be useful to select patients for nonoperative treatment remains to be proven.

Hyponatremia is a common finding in various pediatric patient groups, for example, in children with pneumonia, bronchiolitis, meningitis, and encephalitis and might be regarded as a surrogate marker of disease severity.[24,25] Different patient groups may have different pathogenesis for hyponatremia. However, one important factor they have in common is increased AVP release, although other mechanisms have been proposed.[26] Children with bronchiolitis in the pediatric intensive care unit (PICU) setting may be used as an adequate illustration, since patients with hyponatremia at admission have been shown to have a higher mortality, increased ventilator time, and longer duration of stay in the PICU as compared with children with normal sodium values.[27] The concentration of AVP was also shown to be high in the most severe cases of respiratory syncytial virus-bronchiolitis.[28]

Known nonosmotic stimuli for AVP release associated with AA, and aggravated in perforated AA, are pain, fever, nausea, vomiting, physiological stress, and reduced intravascular volume. Furthermore, perforation of the appendix will initiate peritonitis, with an aggressive inflammatory as well as acute neuroendocrine stress response, stimulating AVP release that in turn may cause low plasma sodium concentration.[29,30] Therefore, we hypothesized that AVP concentration might be increased in these patients. Indeed, patients with perforated AA had significantly higher AVP concentration as compared with patients with no perforation. In our opinion, it is likely that this is a major factor contributing to the lower sodium concentration seen among patients with perforated AA

Plasma sodium concentration is not only highly predictive for distinguishing perforated from nonperforated AA; it is also easily performed at a low cost, and readily available in the pediatric emergency department. In settings where radiographic techniques are not accessible, for example, in resource scarce environments, a strong marker for perforation could possibly impact the care of patients with AA, although this remains to be investigated.

Conclusion

This represents the first prospective study to identify plasma sodium concentration on hospital admission as a predictive marker discriminating perforation from nonperforation in children with AA. In our view, plasma sodium concentration may be used as a supporting tool to supplement clinical examination, blood sampling, and imaging techniques in this setting.

Conflict of Interest

None declared.

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