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ORIGINAL ARTICLE



Blood analysis for screening of electrolyte and kidney function alterations in patients with febrile urinary tract infection

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1 | BACKGROUND

Abstract

Aim: To describe the prevalence, severity, risk factors, and clinical relevance of electrolyte disturbances and acute kidney injury (AKI) during febrile urinary tract infection (fUTI).

Methods: Retrospective observational study of well/fair-appearing patients between 2 months and 16 years, with no previous relevant medical history, diagnosed with fUTI in the paediatric emergency department (PED) with subsequent microbiological confirmation. Analytical alteration (AA) data were considered: AKI (creatinine elevation \times 1.5 the median for age), plasma sodium alteration (\leq 130 or \geq 150mEq/L), and potassium alteration (\leq 3 or \geq 6mEq/L).

Results: We included 590 patients, 17.8% presented AA (13 hyponatremia, 7 hyperkalaemia, and 87 AKI). No patient presented severe analytic alterations or a higher frequency of symptoms potentially attributable to these alterations (seizures, irritability, or lethargy). Risk factors associated with these AA were clinical dehydration (OR=3.5 95% CI: 1.04–11.7; p=0.044) and presenting a temperature >39°C (OR=1.9 95% CI: 1.14–3.1; p=0.013).

Conclusions: Electrolyte and renal function disturbances are infrequent in the previously healthy paediatric population with a fUTI. If present, they are asymptomatic and not severe. Based on our results, performing systematic blood analysis to rule out AA appears no longer justified, especially in the absence of risk factors.

KEYWORDS

acute kidney injury, blood test, febrile urinary tract infection, hyperkalaemia, hyponatremia

Urinary tract infection (UTI) diagnosis is based on the demonstration of leukocyturia and positive urine culture, together with compatible clinical manifestations.¹ However, the indication to perform other

complementary tests in the Paediatric Emergency Department (PED), such as a blood test, is controversial. In general, there is consensus on the performance of blood tests and blood cultures in patients who present with a poor general condition, patients under 2 months of age, and those who have a history of complex uropathy/

Abbreviations: AA, analytical alteration; AKI, acute kidney injury; CRP, C-reactive protein; fUTI, febrile urinary tract infection; PED, Paediatric Emergency Department; PCT, procalcitonin; UTI, urinary tract infection; VUR, vesicoureteral reflux.

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nephropathy.² However, most patients who visit the PED do not meet these criteria. There is currently no consensus among international clinical guidelines as to the need and benefits of performing a blood test in previously healthy patients with suspected febrile urinary tract infection (fUTI).³⁻⁷

On the one hand, acute phase reactants and complete blood count have not demonstrated to be particularly useful in differentiating the anatomical location of UTI.² Moreover, abnormal results in these values are not included as admission criteria in most clinical guidelines.⁸⁻¹¹ Therefore, knowing these parameters would not lead to a relevant modification in the management of these patients.

On the other hand, UTIs are sometimes associated with the deterioration of kidney function.² Furthermore, they can cause electrolyte disturbances such as hyponatremia and hyperkalaemia.^{12,13} These potentially serious alterations can be aggravated by low fluid intake and increased insensible losses due to fever.¹⁴ Therefore, the main utility of blood testing in UTIs may be the detection of patients with electrolyte and kidney function disorders. However, to our knowledge, no robust data described the prevalence and severity of these alterations in the paediatric population. Knowing these data, as well as the clinical-demographic parameters associated with these alterations, could allow the development of consensus and evidence-based protocols to select those patients who could benefit from this test.

This study aimed to describe the prevalence, severity, and risk factors associated with ionic and/or kidney function alterations secondary to fUTI in paediatric patients older than 2months, without previous relevant medical conditions. As secondary objectives, we evaluated the clinical relevance of these alterations in terms of indication of intravenous fluid-therapy for electrolyte or creatinine correction, hospital admission rates, reconsultation rate in the PED in the following 72h after discharge, as well as the rate of hospital admission at the time of reconsultation.

2 | PATIENTS AND METHODS

2.1 | Study design

We performed a retrospective observational study including all patients aged 2 months to 16 years diagnosed with a first or second episode of fUTI in the PED of a tertiary hospital from January 1, 2014, to November 30, 2020.

2.2 | Population/patients

Inclusion criteria were as follows: (1) Patients who met diagnostic criteria for fUTI, (2) patients aged 2 months to 16 years, and (3) patients who underwent a blood test at PED admission.

Exclusion criteria were as follows: (1) Patients with a poor general condition at the consultation, (2) history of recurrent UTI (more than one previous UTI), (3) history of complex genitourinary

Key notes

- Electrolyte and renal function disturbances are infrequent in the previously healthy paediatric population with a febrile UTI.
- If present, they are asymptomatic and not severe.
- Performing systematic blood analysis to rule out these alterations appears no longer justified, especially in the absence of risk factors: high fever (>39°C), and/or clinical dehydration.

malformations (neurogenic bladder, bladder exstrophy, need for intermittent catheterization, monorenal, vesicoureteral reflux [VUR] grade >2, postnatal urinary tract dilatation grade >1 or pathological prenatal kidney ultrasound scans), (4) presence of renoureteral lithiasis, (5) kidney transplant recipients, (6) previous kidney failure, (7) immunodeficient patients, (8) chronic pathology or carriers of multidrug-resistant organisms, as well as (9) patients already diagnosed with fUTI under treatment. The rationale for these exclusion criteria was that in these groups of patients performing a blood test with blood culture is well-established and recommended in all cases. For children with poor general conditions, clinicians have a consensus that additional interventions, such as blood tests and peripheral line placement, are warranted. In our hospital, the general condition of each patient is systematically categorised in the medical records based on subjective assessments by clinicians in good, fair, and poor condition. They consider signs and symptoms such as pallor, cyanosis, altered mental status, lethargy, poor feeding, and decreased responsiveness. However, there is ambiguity regarding the need for additional interventions for children with a fair general condition, as clinical judgement varies among paediatricians. To capture this variation, we included children with a fair general condition in our study, reflecting the real-world scenario where there is no consensus among paediatricians regarding the necessity of blood tests and peripheral line placement in this subgroup.

For patients who had presented more than one episode of fUTI during the study period, we only included the first episode.

2.3 | Variables

Clinical variables analysed were sex, age, fever duration, the maximum temperature reported by the parents or quantified in the PED, vomiting, any degree of clinical dehydration, diarrhoea, poor oral intake, irritability or lethargy, convulsions, general condition (good or fair), and low urine output referred by parents. The outcome variable was the presence of an analytical alteration (AA) defined by sodium, potassium, and creatinine levels. Other laboratory and microbiology variables analysed were C-reactive protein (CRP), procalcitonin (PCT), leukocytes, neutrophils, microorganisms involved, and blood culture positivity. The variables related to clinical relevance 2204

WILEY- ACTA PÆDIATRICA

were hospital admission, intravenous fluid administration, reconsultation rate in less than 72h from discharge, and hospital admission at reconsultation.

2.4 | Definitions

- Febrile UTI: temperature ≥38°C and compatible urinalysis: leukocyturia and/or nitrituria and bacteriuria in significant range in urine collected by a sterile specimen (bladder catheterization >10000CFU/mL, any bacterial count in urine obtained by suprapubic puncture or spontaneous urination >100000CFU/mL).
- Mild urological history: vesicoureteral reflux (VUR) grade I-II or postnatal urinary tract dilatation grade 1.
- Analytical alteration (AA): the presence of at least one of the following alterations:
- Acute kidney injury (AKI): creatinine elevation × 1.5 the median for age.
 - Mild AKI: elevation of creatinine×1.5-1.9 the median for age.
 - Moderate AKI: elevation of creatinine×2-2.9 the median for age.
 - Severe AKI: creatinine elevation × 3 the median for age.
 - Hyponatremia: plasma sodium ≤130mEq/L (moderate: 130– 121mEq/L, severe: ≤120mEq/L).
 - Hypernatremia: plasma sodium ≥150 mEq/L.
 - Hypokalaemia: plasma potassium ≤3 mEq/L.
 - Hyperkalaemia: plasma potassium ≥6 mEq/L (moderate: 6-6.9 mEq/L, severe: ≥7 mEq/L).

The 2012 KDIGO classification of AKI¹⁵ includes in its definitions the basal creatinine, usually unknown in paediatric patients with no previous medical conditions needing blood sampling. This is why we used the median age-adjusted values established by Pottel et al.¹⁶ as the reference creatinine in our study.

2.5 | Study protocol

Our protocol in the PED includes the performance of a blood test with a complete blood count, acute phase reactants, ionogram, and creatinine, as well as a blood culture, in all patients with suspected fUTI in the PED.

2.6 | Statistical analysis

For the descriptive analysis, quantitative variables are presented with centralization and dispersion measures (mean and standard deviation, median and interquartile range, Q1–Q3) and qualitative variables by absolute (N) and relative (%) frequencies. The first analysis compares the two study groups: analytical alteration (AA) and non-alteration (NA), using t-Student for independent samples in parametric continuous quantitative variables and Mann–Whitney U

for non-parametric variables. Frequency analysis between qualitative variables was performed using the chi-squared test, applying Yates' correction in all cases.

Finally, we carried out a multivariate analysis using logistic regression to determine the variables with an independent effect on the presence of AA, controlling for potential confounding factors. Likewise, a multivariate analysis was carried out to identify whether there is an association between AA and a higher hospital admission rate, greater frequency of intravenous fluid-therapy, a higher emergency reconsultation rate, or hospital admission at reconsultation, controlling for potential confounding factors. Statistically significant variables or those with a tendency to significance (p < 0.1) in the univariate statistical analysis and those variables with known clinical relevance were included.

The data were computer-processed using a database in Microsoft Excel format, which was later imported for statistical processing in the SAS program version 9.4 (SAS Institute Inc. 2013. SAS® 9.4 SAS/ STAT Base – Statistical analysis. Cary, NC). Statistically significant differences were defined as those with an error probability of <5% (p < 0.05).

3 | RESULTS

We reviewed the medical records of 1454 patients with a diagnosis of UTI in the PED, of whom 590 patients met the criteria for study participation (Figure 1).

Thirty percent (180/590) of the patients were male, with a median age of 10 (IQR: 15) months. A total of 46 patients (7.8%) had one previous fUTI. Eighteen (3%) had a history of VUR grade \leq II or a postnatal urinary tract dilatation of DTU P1.

The most frequently implicated pathogen was *Escherichia coli* (93.7% of cases), followed by *Proteus* spp. (3.2%). Other less frequent pathogens were *Klebsiella* spp., *Enterococcus* spp., and *Citrobacter* spp., which accounted for 3.1% of the total cases. Of the 525 blood cultures obtained, 12 (2%) were positive, all of them with *E.coli* as the microorganism involved. Seventeen blood cultures (2.9%) identified coagulase-negative *Staphylococcus*, which were considered contaminants.

The analytical blood test results showed a median of PCT 0.4 ng/dL (IQR 1.04), a mean of CRP of 94.6 mg/L (SD 75), leukocytes 18257/mm³ (SD 6728), neutrophils 10289/mm³ (SD 5356), plasma sodium levels 135.7 mEq/L (SD 135.7) and plasma potassium levels 4.4 mEq/L (SD 0.5). The prevalence of analytical abnormalities is shown in Table 1. A total of 17.8% (105/590) of the patients showed AA criteria, of which 13 had hyponatremia (range: 123.2–130 mEq/L) and 7 had hyperkalaemia (range: 6.1– 6.5 mEq/L). AKI was present in 14.9% (87/584), being moderate in 2.1% (12/584) of the patients.

Clinical and demographic characteristics of patients with and without AA are compared in Table 2.

AAs were not associated with vomiting, poor oral intake, low urine output, irritability, lethargy, general condition, shivering, seizures, diarrhoea, or fever duration.



FIGURE 1 Flow diagram to indicate the included and excluded patients.

TABLE 1 Patients' laboratory data.

	N = 590
Neutrophils (>10000/mm ³), <i>n</i> (%)	298 (50.5)
CRP value (>80 mg/L), n (%)	285 (48.3)
Hyponatremia (Na≤130 mEq/L), n (%)	13 (2.2)
Hypernatremia (Na≥150 mEq/L), n (%)	O (O)
Hypokalaemia (K≤3mEq/L), n (%)	O (O)
Hyperkalaemia (K≥6mEq/L), <i>n</i> (%)	7 (1.2)
Mild AKI, n (%)	87 (14.7)
Moderate AKI, n (%)	12 (2)
Severe AKI, n (%)	O (O)

Note: Data are presented as absolute frequencies with the percentage in parentheses.

Abbreviations: AKI, Acute kidney injury; CRP, C-Reactive protein.

There were significant differences between the two groups in terms of age, being older in the group with AA, with a median of 12 months versus 9 months in the group without AA (p=0.011). However, this variable loses significance in the multivariate analysis. The independent risk factors for presenting AA were clinical dehydration, OR=3.5 (95% CI: 1.04-11.7; p=0.044), and temperature elevation above 39°C (OR=1.995% CI: 1.14-3.1; p=0.013). Seventy-seven percent of patients with AA had some risk factor, while 23% had neither fever >39°C nor clinical dehydration (p=0.012). In the absence of these risk factors, the prevalence of AA decreases from 17.8% to 4.1% (p=0.012).

In our sample, no patient presented severe ionic alterations (severe hyponatremia or potassium levels above 6.5 mEq/L) or data of severe AKI, nor did they present a higher frequency of symptoms potentially attributable to these alterations (seizures, irritability, or lethargy).

Nine patients were excluded from the study due to poor general condition; all presented signs and symptoms compatible with septic shock. One had mild acute kidney injury, and another was moderate; none showed sodium or potassium abnormalities. One of them presented bacteremia (11%).

Among the included patients, 24.2% (143/590) were hospitalised, with a higher proportion of patients admitted in the group with AA, 35.2% versus 21.9% in the group without analytical abnormalities (p=0.005). Despite presenting good general condition on arrival to the PED, one patient without AA was subsequently admitted to the paediatric intensive care unit, none with AA. Twenty percent of patients (119/590) received intravenous fluid-therapy in the PED, 31.4% of patients with AA, and 17.7% of patients with NA (p=0.003) (Table 3).

AA were associated with a greater proportion of hospital admission (OR=1.96, 95% CI: 1.18–3.27; p=0.009) and intravenous fluid administration (OR=1.92, 95% CI: 1.13–3.25; p=0.016). Of the 447 patients discharged from PED, 64 (14.3%) reconsulted in the PED, and there were no differences between AA and NA groups. Of these 64 patients, 27 were admitted at reconsultation, 8 with AA and 19 without. There was also no higher risk of hospital admission at reconsultation in patients with AA (Figure 2).

4 | DISCUSSION

In our cohort, 17.8% of the patients with fUTI presented electrolyte disturbances or AKI findings. No patient presented severe abnormalities or a higher frequency of symptoms potentially attributable to these alterations (seizures, irritability, or lethargy). The risk factors associated with these AA were clinical dehydration and presenting a temperature >39°C. Patients who presented AA were admitted to the hospital and received intravenous fluid-therapy in the PED more frequently.

2205

ILEY- ACTA PÆDIATRICA

TABLE 2 Patients' demographic and clinical data.

	No AA (n = 485)	AA (n = 105)	p Values
Age (>24 months), <i>n</i> (%)	387 (79.8)	80 (76.2)	0.42
Gender (female), n (%)	331 (68.2)	79 (75.2)	0.2
Fever duration (>48 h), n (%)	174 (36.1)	48 (45.7)	0.07
Temperature (>39°C), <i>n</i> (%)	310 (64.4)	81 (77.9)	0.008
Previous UTI, n (%)	40 (8.2)	6 (5.7)	0.88
Mild urological history, n (%)	15 (3.1)	3 (2.9)	1
Vomits, n (%)	165 (34)	41 (39)	0.37
Clinical dehydration, n (%)	6 (1.2)	5 (4.8)	0.03
Poor food-intake, n (%)	181 (37.3)	44 (41.9)	0.38
Irritability, n (%)	33 (6.8)	8 (7.6)	0.83
Lethargy, n (%)	30 (6.2)	6 (5.7)	1
Chills, n (%)	31 (6.4)	11 (10.5)	0.14
Diarrhoea, n (%)	28 (5.8)	7 (6.7)	0.65
Seizures, n (%)	2 (0.4)	1 (1)	0.45
Oliguria, n (%)	18 (3.7)	5 (4.8)	0.58

Note: Data are presented as the median, with the interquartile range (IQR) in the parentheses, as the mean with the SD in the parentheses, or as absolute frequencies with the percentage in parentheses. Bold values highlight statistically significant values (this is p < 0.05). Abbreviations: AA, analytical alteration; UTI, urinary tract infection.

TABLE 3 Clinical relevance.

	AA (n = 105)	No AA (n=485)	p Values
Hospital admission, n (%)	37 (35.2%)	106 (21.9%)	0.004
Intravenous Fluid Therapy, n (%)	33 (31.4%)	86 (17.7%)	0.003
Reconsult, n (%)	12 (13.5%)	52 (11.6%)	0.55
Admission in reconsult, n (%)	8 (7.6%)	19 (3.6%)	0.12

Note: Data are presented as absolute frequencies with the percentage in parentheses.

Abbreviation: AA, analytical alteration.

The pathophysiological mechanism by which these AA occur is not fully elucidated. It is considered that AKI is mainly produced by decreased kidney perfusion in the context of hypovolemia secondary to vomiting, poor oral intake, and increased insensible losses produced by fever, which could be enhanced by renal parenchymal damage.¹⁷ In addition to fluid deficiency, there is a tendency to hyponatremia and hyperkalaemia in UTIs, which are presumably related to the syndrome of inadequate antidiuretic hormone secretion and aldosterone resistance caused by proinflammatory cytokines generated in the inflamed renal parenchyma.^{14,18,19}

Interestingly, more than 80% of the patients in our series did not present with AA and could have avoided a blood test. Some guidelines, such as the National Institute for Clinical Excellence (NICE),³ the American Academy of Paediatrics (AAP),⁹ or the (CPS),⁴ do not recommend blood tests for all patients but do not specify when these tests are necessary for patients with fUTI. Others, such as the European Association of Urology/European Society for Paediatric Urology (EAU/ESPU),⁷ recommend routine blood tests for all patients with fUTI. Based on our results, we suggest considering specific recommendations for performing a blood test, as it is an invasive exam, which involves suffering for the patient and his family, prolongs waiting times in the PEDs, and entails an increase in economic costs.

We would expect that the finding of AA during fUTI would be more frequent in younger infants due to their higher percentage of body water and greater kidney immaturity.²⁰ In contrast, our analysis did not identify this association. Patients with AA were slightly older, but age did not prove to be an independent risk factor for these alterations in the multivariate analysis. Based on our results, patients with high fever (above 39°C) and/or clinical dehydration were more likely to present with these alterations, increasing the risk by 2 and 3.5 times, respectively.

In other clinical conditions carrying fluid loss, such as acute gastroenteritis, mild to moderate dehydration does not represent a criterion for mandatory blood testing or intravenous fluid administration. In most of these patients, oral rehydration represents the optimal treatment.²¹ Given our results, considering dehydration is not a frequent finding in patients with fUTI (1.8% of patients) and as almost half of the children with this condition associate AA, it seems reasonable to consider blood testing in this specific scenario. Fever above 39°C is a frequent finding in patients with fUTI (approximately 70% in our series). Although this factor increases the probability of AA by 2 times, only 20.7% of patients with >39°C present AA. The indication to perform a blood test in these patients should be individualised.

The overall prevalence of AA has not been studied to date, although it is postulated that alterations in sodium, potassium, and creatinine are more frequent in patients with fever secondary to UTI than in those with fever for another reason.^{19,22,23} Regarding hyponatremia, it is estimated that up to two-thirds of patients with fUTI have a plasma sodium concentration of less than 135 mEq/L.¹⁴ However, moderate-severe hyponatremia (plasma sodium levels ≤130 mEq/L), which could require specific treatment or could have more relevant prognostic implications,²⁴ has paradoxically hardly been previously studied. In our sample, prevalence of hyponatremia (Na \leq 130 mEq/L) is similar to that found by Pappo et al.¹⁸ with 3.9% of moderate hyponatremia in patients admitted for fUTI. Like our results, they did not identify any cases of severe hyponatremia in the 233 studied children. One potential explanation for the differences obtained in their work may be the inclusion of patients limited to hospitalised children.

Normal potassium levels have a greater variability depending on the age of the patient and the results can be easily altered by the extraction technique as a consequence of haemolysis of the sample.²⁵ Milani et al., in a small sample, described a frequency of hyperkalaemia ($K \ge 6 \text{ mEq/L}$) of 10% in children under 2 years of age with fUTI.¹⁹ In our study, 1.2% of the patients presented hyperkalaemia, and none of them showed a potassium level

ACTA PÆDIATRICA –WILEY

2207





FIGURE 2 Multivariate analysis of risk for hospital admission, intravenous fluid therapy, reconsult in the Emergency Department and hospital admission in reconsult. AA, analytical alteration; CRP, C-Reactive protein.

greater than 6.5 mEq/L. This striking discrepancy could be due to the difference in age between the population samples and to the aforementioned variability of potassium depending on the sample extraction technique.

Regarding kidney function, until now, the prevalence of AKI in previously healthy paediatric patients with fUTI was unknown, with only isolated case reports.^{12,26,27} McGregor et al.²⁸ estimate an incidence of AKI of 5% in non-critical patients hospitalised for any reason. However, this is only an estimation since two creatinine measurements were not available in many of the studied patients. The need for baseline creatinine levels to determine AKI according to the 2012 KDIGO definition¹⁵ makes it difficult to assess previously healthy paediatric patients since this data is generally unknown. In our work, we have used as reference creatinine the median values for each age group established by Pottel et al.¹⁶ According to our cohort, the prevalence of AKI is 14.9%, and it was moderate in 2.1% of cases.

No patient in our cohort presented severe AA. Increased creatinine and mild to moderate electrolyte disturbances are usually asymptomatic. If any symptoms appear, they are nonspecific and overlap with other diseases such as irritability, lethargy, vomiting, and decreased diuresis.^{25,29} We have not found an association between these alterations and the symptoms potentially attributable to them. According to previous studies, approximately half of the patients with a sodium level lower than 125 mEq/L present symptoms of hyponatremic encephalopathy and may develop seizures.³⁰ In our series, 3 patients presented seizures, 2 of whom did not present AA, and one had mild AKI with normal sodium and potassium levels. Only one patient had sodium levels below 125 mEq/L and did not present any type of neurological manifestation.

Predictably, presenting some kind of AA increased the probability of hospital admission and receiving intravenous fluid-therapy in the PED by 1.74 and 1.68 times, respectively. We have no data on the clinical evolution of these patients if intravenous treatment had not been started or if they had not been kept under hospital observation. Presumably, these AA may resolve by treating the infection with oral antibiotics without further intervention although we could not analyse this hypothesis. Patients with AA who were discharged from the PED (68/105) did not reconsult more frequently than those who did not have AA; nor were they admitted more frequently in case of reconsultation.

Due to the retrospective nature of the study, we need to highlight several limitations. First, clinical decisions, such as the indication of hospital admission or the administration of intravenous fluids, varied depending on the paediatrician in charge of the patient, including determining the patient's general condition. We did not assess analytical findings such as hypoglycaemia, metabolic acidosis, etc., and, therefore, were not considered when analysing the clinical relevance of the analytical disorders. However, given that this is a single-center study with a large sample of patients and that well-defined protocols were available and generally used by all PED staff members, we understand that these potential biases would have been minimised. WILEY- ACTA PÆDIATRICA

In our study, data regarding the degree of dehydration could not be collected since most of the clinical records analysed did not include it. Despite this, severe clinical dehydration in our series seems reasonably unlikely, considering that all patients were in good clinical condition. To consider, the method for calculating AKI may be subject to bias, given that creatinine is related to the muscle mass of the individual. However, these reference values according to age are often the only available data in daily clinical practice in PEDs to estimate the deterioration of kidney function.

Moreover, this is a descriptive study, without two arms comparing patients with or without a blood test. We also do not have a randomised comparison between patients with AA who were admitted and those who were not, or those who received intravenous fluids and those who did not. Therefore, based on our data, we cannot give specific recommendations regarding whether it is really necessary to proceed with these therapeutic measures (admission decisions, intravenous fluid-therapy...).

Given that more than 80% of the patients in our series (older than 2 months, without previous relevant medical conditions, or poor general condition) did not present AA, and if present, they are asymptomatic and not severe; it does not seem justified to routinely perform this test to screen for electrolyte and renal function alterations, especially in patients with no risk factors. In the absence of high fever (>39°C), and/or clinical dehydration, the prevalence of AA decreases from 17.8% to 4.1%. Avoiding unnecessary blood tests would represent a significant economic saving and reduce the overload of care in the PEDs. It would also prevent the paediatric patient from suffering blood extraction.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest or financial relationships relevant to this article to disclose.

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2209