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The importance of bioelectrical impedance in the critical pediatric patient

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SUMMARY

Background & aims: Sepsis is still a significant cause of death in the Intensive Care Unit and its early diagnosis is vital. Changes in cell permeability have been observed early in sepsis. Lower values of bioelectrical impedance (BIA) such as reactance adjusted by height (Xc/H) and phase angle (PA) have already been studied as a prognostic biomarker for many diseases and may indicate cell injury. BIA is a low cost, practical, noninvasive method that can be measured at bedside. This study investigated the utility of PA and Xc/H raw values in the pediatric critical care unit as predictors of progression to septic shock, as a clinical monitoring tool and to support the diagnosis of septic shock.

Methods: We prospectively analyzed bioelectrical impedance in 145 children aged between one month and six years who were not in septic shock on admission to the intensive care unit Serial bioelectrical impedance analysis (BIA) measures were analyzed to determine the sensitivity and specificity of accurately identifying children who subsequently developed septic shock. Kaplan-Meier septic shock-free survival curves modeled by Xc/H and PA were done.

Results: The free-septic shock survival curve analysis showed that patients with the lowest median values of Xc/H and PA were associated with the highest percentage of occurrence of septic shock ($p = 0.0001$ for Xc/H and <0.0006 for PA) and longest length of stay in the intensive care unit ($p < 0.0011$ for Xc/H and $p < 0.004$ for PA). Values of Xc/H below 48.63 Ohm/m at admission showed statistically significant odds ratio (OR) of 3.72 for developing septic shock any time during the hospitalization period, with a 87% sensitivity, 35% specificity and an area under the curve (AUC) of 0.62. The PA at admission did not show significant results. During hospitalization, patients with Xc/H below 35.72 Ohm/m were 3.38 times more likely to develop septic shock in the next day, with a sensitivity of 66.7%, a specificity of 62.3% and AUC of 0.65. PA values below 3.27 had an OR of 9.58 for a septic shock the next day with a sensitivity of 95.8%, specificity of 29.4% and AUC of 0.62. The presence of a value of Xc/H below 33 Ohm/m showed a strong association with the occurrence of septic shock on the same day of the measurement, with an OR of 11.7, as well as a value of PA below 2.64, showed an OR of 14.2.

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Conclusions: The bioelectrical parameters Xc/H and phase angle have limitations in predicting septic shock as isolated biomarkers, but have a potential role as a monitoring tool in the pediatric intensive care unit. The comparative value with other biomarkers remains to be elucidated.

1. Introduction

Despite advances concerning support and treatment, sepsis is still a significant cause of death in the Intensive Care Unit [1]. The diagnosis of sepsis is still a challenge, since there are no clinical-laboratory criteria, biological markers, radiological or imaging diagnosis that could, individually or jointly, unequivocally identify a patient with sepsis [2]. The two significant difficulties in treating sepsis are failure to recognize the early stages of the disease and underestimation of its severity [3]. It is still difficult to determine which patients with signs of infection at a first evaluation will develop a more severe form of the disease.

In the last decades, several biomarkers have been proposed for the diagnosis and prognosis of pediatric septic patients [4]. A study comparing 18 children with sepsis and 23 with SIRS showed that resistin, extracellular heat shock protein 90α and lactate achieved an area under the receiver operating characteristic curve greater than 0.80 to discriminate sepsis from systemic inflammatory response [5]. Another study found lower levels of ATP on day 1 in septic children than in children with SIRS [6]. Concentrations of procalcitonin revealed in a study good discriminative power to predict septic shock with an area under the receiver operating characteristic curve of 0.91[7]. Bioelectrical impedance is a low cost, practical, noninvasive method that can be measured at the bedside.

It is a non-painful exam that also does not despoil blood that may be particularly important for quality of care especially in young children. Because it is a low-cost exam that does not require a laboratory team or expensive supplies, it is especially attractive to intensive care units with limited financial resources, such as in non-developed countries. The components to be measured are resistance and reactance. Resistance (R) refers to the restriction to the flow of an electrical current through the body, primarily related to the amount of water present in tissues. Reactance translates the interface between the tissues and the cell membrane, which can store energy, acting as a capacitor. The phase angle (PA) is a component mathematically obtained from the resistance and reactance, interpreted as an indicator of the membrane integrity, and is pointed as a marker of prognostic value, which suggests that PA can be an important instrument to estimate clinical results or monitor critically ill patients [8]. Higher PA values show greater cell membrane integrity and function, and are thus related to cellular health [9]. The state of sepsis causes profound changes between the content of lean body mass, total body water and its distribution [10]. The increased capillary permeability and rupture of the membrane in sepsis are responsible for the leakage of liquid, development of third space and hyperhydration of the lipophilic portion of the cell membrane [10]. Da Silva et al. studied 95 adults in the intensive care unit and observed a moderate association of phase angle with the prognostic score APACHE II (Acute Physiology and Chronic Health Evaluation) in patients without sepsis [8]. A recent study involving children who underwent cardiac surgeries showed that low PA values (<2.7) were correlated with longer hospitalization times (>4 days) [11]. Therefore, those studies suggest that low PA values can be associated with clinical conditions of poor prognosis.

This study investigated the utility of raw values of Phase Angle (PA) and reactance normalized by height (Xc/H) in the pediatric critical care unit. Those components were investigated as predictors of developing septic shock, as a monitoring tool and as an instrument to support the diagnosis of septic shock.

2. Materials and methods

A group of consecutive patients was supervised from admission to discharge at the Pediatric Intensive Care Unit of the *Instituto Nacional Fernandes Figueira* (IFF)/Fiocruz. IFF is a federal tertiary hospital without an emergency room, therefore most critical patients are referred from other healthcare units. Patients were included if they were aged between one month and six years and excluded if they weighed less than 3 kg, already had septic shock, were chronically hospitalized (for more than three months), if it was not possible to obtain bioelectrical impedance parameters within the first 24 h of admission or if they were admitted at ICU exclusively for monitoring reasons. Eligible patients admitted to the ICU more than once during the study period were included only on their first admission. The study was reviewed and approved by the Institution's Ethics Committee for Research with Human Subjects.

Bioelectrical impedance was measured daily until discharge or death, up to a maximum period of 14 days, with the first measurement in the first 24 h of admission in the intensive care unit. Bioelectrical impedance parameters Resistance (R) and Reactance (Xc) were obtained with a portable monofrequential plethysmograph BIA 101 Quantum II (RJL Systems, USA), calibrated weekly with a circuit of known impedance value provided by the manufacturer. This equipment works at the single frequency of 50 kHz. Means of triplicate measurements were used in the analysis. The measurement procedure was conducted using the standard tetrapolar electrode distribution [12]. The inner electrode arm (sensor) was placed on the dorsal surface of the right wrist between the ulna and the radius. The leg electrode was placed on the anterior surface of the right ankle between the protruding portions of the bones. The external electrodes (source or injector) were placed on the dorsal surface of the third proximal phalanx of the right hand and right foot. In the infants, the position of the injector electrode was the same but the sensor electrode was moved proximally, leaving 5 cm of free skin between them, the minimal distance required to avoid interaction between electric fields, which could otherwise lead to an overestimation of impedance values [13]. Bioelectrical impedance PA was calculated from the arctangent of the ratio of Xc to R at 50 kHz (PA = arctg (Xc/R). Reactance values were adjusted for height, yielding Xc/H [14]. All measurements were performed by five investigators (ZA, MS, FL, EP and MJ), who were not blinded to patient clinical data.

Demographic variables analyzed were: age in months, gender and ethnicity. The classification of ethnicity used in this study was from the Brazilian Institute of Geography and Statistics (IBGE) that defines individuals as white, black, brown, yellow and Amerindian based on phenotypic criteria [15]. Clinical variables investigated the presence of comorbidities, anthropometric data, nutritional status, edema, two mortality risk scores (the Pediatric Risk of Mortality [16] - PRISM and the Pediatric Index of Mortality [17]- PIM 2) and

sepsis severity (systemic inflammatory response syndrome, sepsis, severe sepsis or septic shock. Regarding nutritional status, patients were classified according to WHO 2006 curves cutoff criteria based on weight/age or height/age depending on the age of the subject: up to two years-old, the cutoff value for defining a child as malnourished was z score ≤ -2SD of the weight/age curve or height/age curve; above two years of age the cutoff value was the z score $\leq -$ 2SD of the height/age curve [18]. The sepsis severity and MODS classification followed the criteria from the International Pediatric Sepsis Consensus Conference [19] and acute respiratory distress syndrome (ARDS) was defined according to the American European Consensus Conference definition [20]. Cardiogenic patients were defined as those requiring invasive mechanical ventilation for cardiac reasons, such as pulmonary hyperflow, congestive cardiac failure or congenital heart disease. Patients who did not show pulmonary injury but were submitted to mechanical ventilation for other reasons were defined as support. Accordingly, sepsis was defined as the presence of Systemic Inflammatory Response Syndrome (SIRS) plus a suspected or proven infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. The diagnosis of SIRS needs the presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count: a) core temperature >38.5 °C or <36 °C; b)tachycardia, defined as a mean heart rate >2SD above normal for age in the absence of external stimulus, chronic drugs or painful stimuli; or otherwise unexplained persistent elevation over a 0.5–4 h time period or for children <1 year-old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, beta blocker drugs or congenital heart disease or otherwise unexplained persistent depression over a 0.5 h time period. C) mean respiratory rate > 2SD above normal for age or mechanical ventilation for an acute process unrelated to underlying neuromuscular disease upon receipt of general anesthesia; D) elevated leukocyte count or depressed for age (not secondary to chemotherapy-induced leucopenia) or 10% immature neutrophils. Septic shock is defined as sepsis in the presence of cardiovascular dysfunction. The classification of sepsis and septic shock were adjudicated by one pediatric intensive care investigator (ZMAA), who was not blinded to the bioelectrical impedance measurements.

Categorical variables were summarized as frequencies and proportions, and continuous variables as medians and interquartile ranges.

The differences of bioelectrical impedance parameters at admission between the patients that progress or not to septic shock during hospitalization were analyzed with the Mann-Whitney test.

The usefulness of PA and Xc/H in the Intensive Care Unit will be investigated from the analysis of these variables as predictors, as a monitoring tool and in the diagnosis support. The outcome of interest is a septic shock at any time during hospitalization.

The predictive capacity of PA and Xc/H will be analyzed from their measured values at admission and 24 h before the occurrence of the septic shock outcome. We plotted the receiver operating characteristic (ROC) curves and selected as the best cutoff the point with maximal Youden's J statistic [21]. We adopted this cutoff to calculate sensitivity, specificity and odds ratio (OR). The prediction parameters (24 h before the occurrence of the septic shock) entailed multiples tests per patient and were based on the probabilities of outcome estimated by generalized estimating equations (GEE) models with binomial family, logistic link function and Huber-White robust standard errors. We selected GEE's correlation structure based on the minimization of the Quasi-likelihood under the independence model criterion (QIC).

The longitudinal evaluation of the daily measurements facilitated the understanding of the role of bioelectrical impedance as a monitoring tool. A septic shock-free survival curve analysis was employed to assess whether patients with lower values of Xc/H and PA showed more septic shock events. First, the medians of Xc/H and PA were calculated for each patient. Then, patients were divided into four groups, referring to the quartiles of the medians of Xc/H and PA. The Kaplan-Meier estimator was employed in the survival analysis, stratified by the quartiles of bioelectrical impedance values (Xc/H and PA). We used the log-rank test to analyze the difference in survival among different groups. Ninety-five percent confidence intervals were used for all point estimates.

The association of bioelectrical parameters with the occurrence of septic shock on the same day was also investigated to evaluate the possibility of using these parameters as a tool to support the diagnosis. The probabilities of outcome estimated by generalized estimating equations (GEE) models with binomial family, logistic link function and Huber-White robust standard errors.

All analyses were performed using the statistical software Stata (version 14.2. StataCorp: College Station, Tx. 2015) and the user-written routines *senspec* [22] and *somersd* [23,24]

3. Results

3.1. The clinical and demographic profile of patients included in the study

A total of 145 infants and preschool children from 29 days to 83 months of age, with a median age of 8.4 months (IQ 3.4–23.4), admitted to the Pediatric Intensive Care Unit (UPG-IFF/FIOCRUZ) between 15/02/2013 and 03/09/2015 were studied, totaling about two years and seven months of study. Gender distribution evidenced the predominance of boys (60%). The predominant ethnicity was brown (n = 71; 49%) followed by white (n = 48; 33%) and black (n = 26; 17.9%). Regarding nutritional status, most patients in the study were eutrophic (69.7%), with only 23.4% malnourished, 2.8% obese, and 4.1% overweight. We have not observed a statistically significant association between phase angle and malnourished children. The mean phase angle at admission was 2.97 in malnourished children and 2.95 in eutrophic children (p-value = 0.86).

The PIM2 median was 1.7 (1–5.4) and the PRISM was 7.0 (3.3–11). Median hospital stay length was seven days (4–12 days). Eighty-five patients were submitted to mechanical ventilation with a median ventilation time of 6 days. Table 1 summarizes some clinical characteristics of the patients included in the study.

3.2. The predictive capacity of admission bioelectrical impedance parameters for septic shock

We observed that at admission, the median values of Xc/H were 36.72 (28.54–43.11) and PA were 2.61 (2.44–3.20) in those who developed septic shock any time during the stay in the intensive care unit. Those who never experienced septic shock during the stay in the intensive care unit had median values of Xc/H of 40.53 (33.62–54.40) and of PA of 2.90 (2.60–3.50). These differences were not statistically significant (p-value = 0.05 and 0.06, respectively).

Table 2 shows the performance of PA and Xc/H at admission in predicting the occurrence of septic shock during hospitalization in the intensive care unit. We found that values of Xc/H below 48.63 Ohm/m at admission presented a statistically odds ratio with a good sensitivity but with low specificity and weak area under the curve (AUC). The PA at admission did not show significant results (Table 2).

Table 1
Clinical profile of studied patients hospitalized at UPG-IFF/FIOCRUZ from 2013 to 2015.

Characteristics	N = 145	%
Sepsis severity (greater severity)		
No SIRS, no sepsis	9	6.2
SIRS	7	4.8
Sepsis	89	61.4
Severe sepsis	16	11.0
Septic shock	24	16.6
Lung injury severity (greater severity)		
No lung injury	25	17.2
Support	26	17.9
ALI	71	49.0
ARDS	15	10.3
Cardiogenic edema	8	5.5
Nº organ dysfunctions (greater severity)		
0	30	20.7
1	74	51.0
2	27	18.6
3	10	6.9
4	3	2.1
5	1	0.7
6	0	0
Comorbidities		
Present	83	57
Absent	63	43
Outcome		
Survivors	140	96.5
Nonsurvivors	5	3.4
Admission causes		
Respiratory	110	75.8
Gastrointestinal	18	12.3
Neurological	10	6.9
Cardiological	3	2.0
Oncohematological	2	1.4
Endocrine	1	0.7
Other Infectious Diseases	1	0.7

Notes: SIRS = Systemic Inflammatory Response Syndrome.
ALI = Acute Lung Injury.
ARDS = Acute Respiratory Distress Syndrome.

3.3. Performance of Xc/H and PA in predicting septic shock 24 h before its occurrence

The Xc/H values below 35.72 Ohm/m were 3.38 times more likely to develop septic shock in the next day, with a sensitivity of 66.7% and a specificity of 62.3%. The AUC of 0.65 represents a low discriminatory power. PA values below 3.27 had a significant odds ratio of 9.58 for septic shock with a high sensitivity of 95.8% but with a low specificity of 29.4%. The AUC was also unsatisfactory (Table 3).

Table 2
Predictive capacity of Xc/H and PA obtained at admission to anticipate the occurrence of septic shock during hospitalization.

Class	Septic shock	
No observations	145	145
Test[a]	Xc/H	PA
AUC (95% CI)	0.62 (0.50–0.74)	0.62 (0.50–0.74)
Cutoff	48.63	2.78
Sens (95%CI)	0.87 (0.67–0.97)	0.58 (0.36–0.78)
Spec (95%CI)	0.35 (0.26–0.44)	0.63 (0.54–0.71)
OR (95%CI)	3.72 (1.12–12.4)	2.36 (0.98–5.69)

Note: AUC = area under curve; sens = sensitivity; spec = specificity; OR = odds ratio.
[a] The cutoff values were chosen based on maximal Youden's J statistic.

3.4. Association of Xc/H and PA and the occurrence of septic shock on the same day

The values of Xc/H below 33 Ohm/m on the day of septic shock had a significant odds ratio of 11.7, with a sensitivity of 83%, but with low specificity. Similarly, values of PA below 2.64 showed a strong association with the occurrence of septic shock with a significant odds ratio of 14.42, a sensitivity of 87.5%, but with low specificity (Table 3).

3.5. Survival curve for the occurrence of septic shock according to Xc/H and PA values

Figure 1 shows the septic shock-free survival curve of the four groups, referring to the quartiles of the medians of Xc/H and PA. The behavior of the first group curve with lower values of Xc/H (Xc/H = 13.67–31.80) and phase angle (PA = 1.64–2.62) was statistically different from the others 3 quartiles groups (Xc/H = 31.81–84.12; PA = 2.63–4.75), with p = 0.0001 and p = 0.0006, respectively. In the lowest quartile of Xc/H, 62.2% were free of septic shock (14 patients developed septic shock from a total of 37 patients while in the three other quartiles 90.8% of the patients were free of septic shock (only 10 patients developed septic shock from a total of 108 patients).Similarly, in the lowest quartile of PA, 64.9% of the patients were free of septic shock (13 patients evolved with septic shock from a total of 37), while 89.8% did so in the other three quartiles (only 11 patients from a total of 108 developed septic shock in this group). The group with the lowest values of Xc/H (14,37–31,11) had a median of 13 hospitalization days (7–21 days) while the values of Xc/H $\geq$ 31.12 had a median of seven hospitalization days (4–10.5 days) that was statistically significant (p = 0.004). Similarly, the group with lowest phase angle values (1.6–2.6) showed longer hospitalization times, with a median of 12 days (7–21), when compared to the group with phase angle $\geq$ 2.61, which had a median of 7 days (4–10.5), and this difference was also statistically significant (p = 0.001).

4. Discussion

This study found that bioelectrical parameters (Xc/H and phase angle) showed limited value as predictors for septic shock. However, the results of this study showed that the bioelectrical impedance test could be useful for monitoring critically ill patients. Analysis of the septic shock-free survival curve showed that the group of patients who persisted with low values of Xc/H and PA showed a different behavior than others, and was associated with a higher percentage of occurrence of septic shock and with longer hospitalization times. This means that those patients who fail to recover Xc/H and PA values, despite intensive care unit treatment, are associated with more significant complications. A similar result had already been established in a previous study that showed that Xc values increased significantly between admission and discharge among survivors, whereas showed a declining trend among nonsurvivors between admission and death [25].

Phase angle has already been studied as a health marker in various disease conditions [10]. In this study, we found that bioelectric parameters, PA and Xc/H at admission showed values lower than previous values in the literature to healthy children. A previous study of our group, with children from the same geographic area of this study, found higher values of Xc/H (46–52 Ohms/m) and PA (3.2°–4.0°) in healthy children in the range of 1 month–36 months [26]. A study involving 113 Dutch children up to 1 year of age showed higher values of Xc/H (63 Ohm/m at two months and 73

Table 3
Performance of Xc/H and PA (phase angle) values in anticipating the diagnosis of septic shock in 24 hours and to support the septic shock diagnosis on the day of the event.

	24h before the occurrence of septic shock	In the day of septic shock
Nº of days observed	670	815
Test	Xc/H	Xc/H
AUC (95% CI)	0.65 (0.55–0.75)	0.76 (0.69–0.84)
Cutoff	35.72	33
Sens (95%CI)	66.7 (44.7–84.4)	83.3 (62.6–95.3)
Spec (95%CI)	62.3 (59–66.6)	70 (66.7–73.2)
OR (95%CI)	3.38 (1.46–7.84)	11.7 (4.13–33)
Test	PA	PA
AUC (95% CI)	0.62 (0.58–0.67)	0.77 (0.70–0.84)
Cutoff	3.27	2.64
Sens (95%CI)	95.8 (78.9–99.9)	87.5 (67.6–97.3)
Spec (95%CI)	29.4 (25.9–33.1)	67 (63.3–70.3)
OR (95%CI)	9.58 (1.29–71.47)	14.2 (4.47–45.1)

AUC = area under curve; sens = sensitivity; spec = specificity; OR = odds ratio.
*The cut off values were chosen based on Youden method [21].

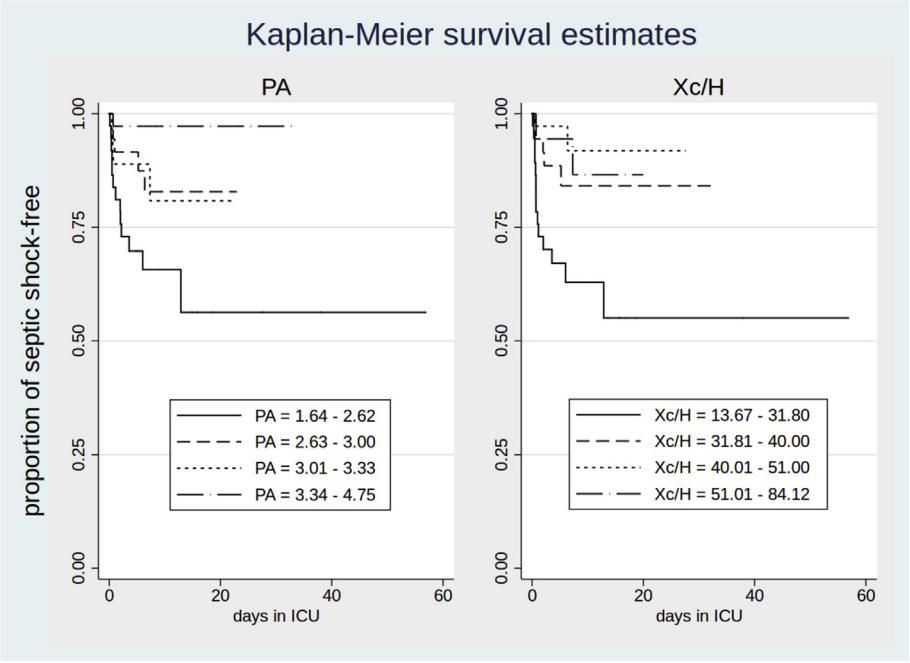

Fig. 1. Kaplan-Meier septic shock-free survival curve modeled by phase angle and Xc/H.

Ohm/m at 8–12 months of life) [27]. Savino and colleagues studied 153 Polish children up to 1 year of age and found a mean Xc/H of 41 Ohm/m and a phase angle of 2.9° [28]. A large Italian population study including 2044 healthy children between 2 and 15 years of age showed mean values of Xc/H of 37–60 Ohm/m and phase angle between 4.6 and 6.2°, both varying according to age [29].

Regarding predictive capacity, only Xc/H values at admission were statistically significant for septic shock. Thus, the Xc/H values at admission may appear an attractive option of screening exam because of its high sensitivity of 87%. However the specificity of 35% is very low. Therefore, as an isolated biomarker, Xc/H at admission as predictor of septic shock has limitations.

When analyzing the capacity of Xc/H and PA values to anticipate severe outcomes 24 h before the event, children with values of Xc/H $\leq$ 35.72 showed a significant odds ratio of 3.38 to predict septic shock. A lower cutoff point was verified on the day before the event for Xc/H than the one observed at admission. Children with values of Phase angle $\leq$3.27 also showed significant odds ratio of 9.58 with a high sensitivity of 95.8%. So, children with a PA >3.27 were less likely to develop septic shock.

Analysis of the Xc/H data shows better performance as a day-of-event diagnostic test for septic shock. This discloses Xc/H as an objective marker that can serve as a tool to ensure a more precise diagnosis of septic shock. Despite the increasing awareness of the importance of early diagnosis and appropriate treatment for patients with sepsis, many patients still do not receive early care [2]. It is recognized that early diagnosis of sepsis is vital and, once detected, its care must be initiated quickly and effectively, always keeping in mind that time is crucial [30]. However, a test that establishes the diagnosis of sepsis or septic shock is not available. Both sepsis and septic shock are diagnosed based on signs, symptoms and laboratory changes that indicate their presence [19]. This raises concerns to the pediatrician, since some criteria conditions such as fever, leukocytosis and tachycardia are present in common,

uncomplicated infections [31]. The Third International Consensus on Sepsis reviewed its definition. However, the task force focused only on adult patients and recognized that definitions of pediatric sepsis must also be updated taking into account variations in the physiological and pathological values that are age dependent [2]. An objective exam that helps the physician in this septic shock diagnosis can be important especially when it occurs before the patient arrives at intensive care services that is equipped with a more qualified professional for this diagnosis. The admission in our intensive care unit of an existing significant proportion of children with septic shock also reflects the precariousness of diagnosis, resulting in a late referral. The role of early bioelectrical impedance, in the emergency sector has yet to be established. Considering poor availability of beds in public pediatric intensive care units in the face of the demand, an analysis to streamline these beds is of utmost importance in the socio-political context, mainly in countries with limited resources.

Some limitations of this study should be highlighted. The study was conducted in a closed unit within the Fernandes Figueira National Institute, which has no emergency service. Due to current public health, a determining factor in limiting the sample was that many children hospitalized in the study period had were already been admitted with septic shock and could not be included in the study Thus, the evaluation of mortality as an outcome was also compromised, since the percentage of death was low, accounting for only 3.4% of the patients. These results would have to be confirmed in other pediatric intensive care units with differentiated profiles. Another limitation was that when comparing a septic shock group with a group without septic shock, the group without septic shock may evidence other severe conditions, such as the presence of ARDS or MODS that somehow modify cellular integrity and could result in low reactance and phase angle. Therefore, a multivariate analysis controlling those variables seems to be essential to increase the performance of the test, which will require a larger sample. Future research will also be required to compare the performance of bioelectrical parameters with other existing biomarkers and thus determine their practical value [5–7].

The results shown lead authors to conclude that the use of bioelectrical parameters (Xc/H and phase angle) to predict development of septic shock has huge limitations as an isolated biomarker. These parameters have a potential role to support the diagnosis of septic shock, and although there is no way to replace the current criteria, it can be an objective tool to avoid delays in the diagnosis, especially from the non-intensive care physicians. The authors believe that bioelectrical parameters should be remembered in studies that address formulas with multivariate analysis to meet that need. The authors found a potential role for these parameters as a monitoring tool that requires further studies.

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Statement of authorship

Z.A. conceived and coordinated the study. Z.A, M.J., E.P., F.L. and M.S performed the bioimpedance exam. Z.A.,D.C. and F.L were responsible for the accuracy of the clinical data and classification of severity according to the Consensus. D.M., M.S., E.P. were responsible for inspection and correction of collected data. D.M. was responsible for writing the first draft of the manuscript. E.R. designed the database. B.S and E.R. performed statistical analysis. Z.A., D.M., E.R., B.S. participated in the discussion and interpretation of the results. All authors read and approved the final version.

Conflicts of interest

The authors disclose no conflicts of interests.

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