

# SBI is uncommon in the absence of paediatricians' gut feeling and abnormal respiratory pattern

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## Abstract

**Aim:** According to the Italian national statistical institute, severe bacterial infections (SBI) in Italy are responsible for 1.7% of mortality under 5 years of age and their recognition is often challenging, especially in the first stages of the disease.

We tried to estimate the prevalence of SBI in our target population and to identify signs and symptoms that could guide in the initial evaluation of a child with a possible SBI.

**Methods:** We designed a prospective, multicentre study and enrolled patients aged 0–14 years at the first evaluation to the emergency department with an acute illness lasting a maximum of 5 days. The presence of variables suggestive of SBI was collected for every enrolled patient. One week after the enrolment, every patient was followed up by telephone.

**Results:** SBI is more likely to be detected with the 'gut feeling' in both univariate and multivariate models (univariate OR: 7.16, 95% CI: 4.08–12.56; multivariate OR: 5.34, 95% CI: 2.78–10.25), while abnormal breathing pattern resulted significant only in univariate model (OR 3.83, 95% CI: 1.98–7.40). Nevertheless, their associated sensitivity is low.

**Conclusion:** SBI is uncommon in the absence of paediatricians' gut feeling and abnormal respiratory pattern.

## KEYWORDS

abnormal respiratory pattern, emergency department, gut feeling, paediatric patients, severe bacterial infection

## 1 | INTRODUCTION

Severe bacterial infections (SBI), that is, meningitis, pneumonia, pyelonephritis, gastroenteritis, osteomyelitis, cellulitis/abscess and

sepsis, are associated with worldwide high mortality and childhood morbidity rates.<sup>1–4</sup> In Italy, SBIs are responsible for 1.7% of infant mortality under 5 years of age.<sup>5</sup> In Europe, the incidence of severe infections observed at primary care services in children aged

**Abbreviations:** CI, confidence interval; ED, emergency department; IQR, interquartile ranges; MOFICHE, Management and Outcome of Febrile children in Europe; NICE, National Institute for Health and Care Excellence; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; ROC, receiver operating characteristic; SBI, severe bacterial infection; Se, sensitivity; Sp, specificity; YOS, Yale Observation Scale.

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0–14 years is around 1% per year.<sup>6,7</sup> In emergency departments (ED), this percentage reaches 25% due to fever without localisation and to the fact that patients that access to the ED usually present more severe disease than their prehospital counterpart.<sup>8</sup> According to this evidence, a paediatrician both in primary care services and emergency departments may face at least 2–3 severe infections every year. Due to the lack of typical 'textbook signs' (altered state of consciousness, altered perfusion, signs of meningeal irritation, cyanosis, petechiae and convulsions) in the first stages of the disease, the prompt recognition of an SBI is often challenging.<sup>6,9</sup>

Moreover, in the ED setting, a triage performed by staff who lack paediatric experience or clinical evaluations in crowded environments with many accesses could be possible further sources of error.<sup>9</sup> Furthermore, signs and symptoms in the early stages of an SBI could be very subtle, resulting in delayed management.<sup>10,11</sup> The main challenge for the triage nurse and the paediatrician is, therefore, the early recognition of those clinical conditions in which the risk of a severe evolution cannot be excluded. According to previous studies, some specific historical and physical clues, such as physicians' gut feelings, parents' perceptions or dyspnoea, may help promptly recognise children at risk for severe infections in an outpatient setting.<sup>6,7,9</sup> Nevertheless, the effectiveness of these signs has been poorly investigated in an ED setting. The aim of our study was to assess the predictive value of 'first look' signs and symptoms for SBI in the paediatric ED setting.

## 2 | MATERIALS AND METHODS

We designed a prospective, multicentre study approved by the Independent Committee for Bioethics of the Institute for Maternal and Child Health, IRCCS 'Burlo Garofolo', Trieste, Italy (RC 10/16 prot 620/2016).

The study was conducted in the paediatric ED of the Institute for Maternal and Child Health IRCCS Burlo Garofolo of Trieste, Italy, and the 'Ospedale Santa Maria degli Angeli' of Udine, Italy.

Patients aged 0–14 years at the first evaluation to the ED with an acute illness lasting a maximum of 5 days were considered eligible for the study. Acutely ill patients presenting the classical textbook signs of SBIs, such as symptoms of meningeal irritation, refill time > 2", cyanosis, petechiae and seizures, were excluded from the enrolment. Patients already seen in the ED for the same acute illness were excluded, as well as children with known chronic diseases, including cystic fibrosis, congenital heart disease, inflammatory bowel disease and infantile cerebral palsy. Patients with immune deficiencies or assuming immunosuppressive therapies were also excluded.

### 2.1 | Index clinical signs

A specific electronic form was developed to collect data. The questionnaire had to be completed at the end of the first clinical examination by the physician in charge of the visit.

### Key Notes

- Severe bacterial infections (SBI) are associated with worldwide significant mortality and childhood morbidity rates. A paediatrician may face 2–3 severe infections every year.
- Due to the usual lack of typical textbook signs in the first stages of the disease, the prompt recognition of an SBI is often challenging.
- 'Gut feeling' and 'abnormal breathing pattern' are highly relevant in considering the high risk for SBI.

For every enrolled patient, the presence or absence of the following variables was collected:

- The clinician's perception of the patient's illness, the so-called 'gut feeling', was defined as a subjective feeling that something was wrong with the patient and he/she was at risk of an SBI.<sup>12</sup>
- Parent's perception of the child's illness based on the report given during the visit, such as 'not the usual fever, like a seasonal viral disease' or 'my child's behaviour is not usual'.
- Altered respiratory pattern: it included the evaluation of breathing abnormalities: the presence of tachypnoea, defined as several respiratory acts major than 97<sup>th</sup> centile for ages and corrected for temperature value<sup>13</sup>; respiratory distress, defined by intercostal, subdiaphragmatic and supraclavicular retractions, use of abdominal muscles; and grunting.
- Presence of fever equal to or above 39.5°C during the acute illness and fever with shivering.
- Presence of diarrhoea.
- Tendency of patient's immobility or obligated body position.
- The respiratory and cardiac frequency and body temperature detected at triage were reported for each patient.
- Leading symptom at triage.
- Preliminary ED diagnosis.

The variables mentioned above were chosen according to previous specific literature.<sup>7</sup>

One week after the enrolment, every patient was followed up by telephone. Parents were asked about the resolution of the acute infectious episode, response to the empirical antibiotic therapy when started, return or referral to the ED for clinical deterioration, the persistence of symptoms, further investigations, hospitalisation and starting/changing antibiotic treatment.

The follow-up was performed by two independent researchers who formulated a final diagnosis, completing the electronic record. The clinicians performing the initial ED evaluation were blinded regarding the follow-up and the final decision about the presence of an SBI. SBIs cases were reviewed and discussed in case of doubt.

The following conditions were classified as SBIs: sepsis/bacteraemia, meningitis, pneumonia, bacterial gastroenteritis, osteomyelitis, complicated acute otitis media (otomastoiditis and intracranial complications), pyelonephritis and cellulitis/abscess. The diagnosis of SBIs had to be supported by every data available since no single clinical sign, or diagnostic test can provide the certainty of the diagnosis of SBI. Therefore, we considered everything we had: anamnesis, physical examination, clinical picture and evolution, laboratory investigations (blood count, C-reactive protein and culture tests), radiological imaging and treatments administered at home or during hospitalisation when needed.

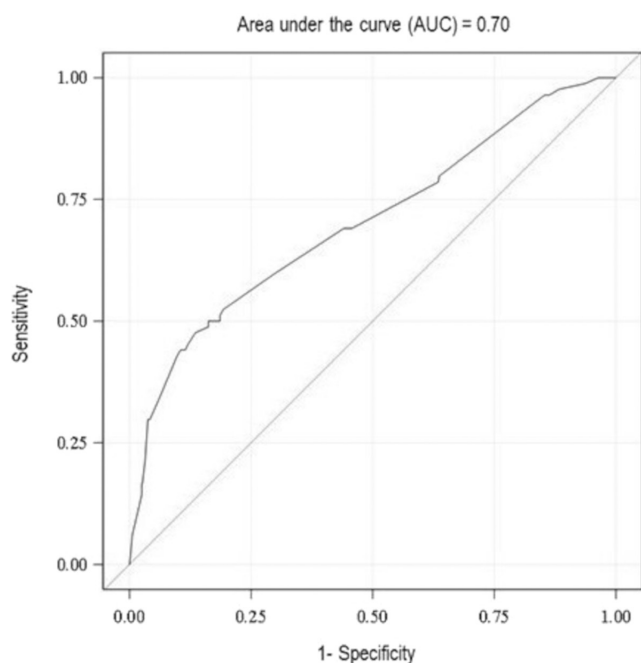


FIGURE 1 ROC curve. Predictive value of the model to stratify the risk of severe bacterial infections

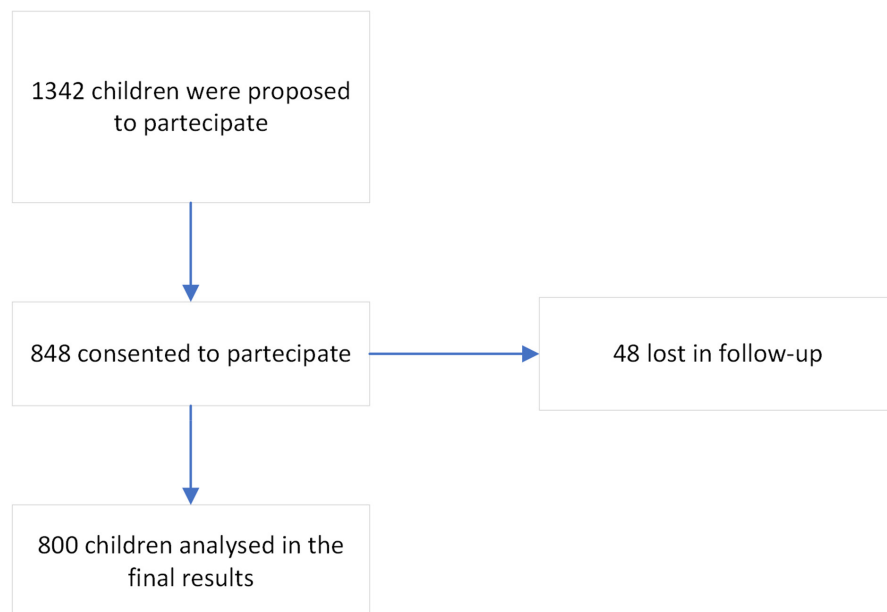


FIGURE 2 Flow chart of the study design

## 2.2 | Statistical analysis

A sample size of 800 children was calculated, based on the proportion of a prevalence of SBI in the ED setting of 25%, error margin of 3% with 95% confidence level.

Continuous variables were reported with medians and interquartile ranges (IQR, 25th–75th percentile), while categorical variables were presented as numbers and percentages.

Associations with SBI identifying variables were evaluated using the nonparametric Wilcoxon–Mann–Whitney test for continuous variables and chi-square or Fischer exact test for categorical variables.

Sensitivity, specificity and positive and negative predictive values were calculated applying univariate and multivariate logistic regression models, adjusting for age class. The dependent variable was the SBI group, while independent variables were determined by applying the stepwise selection method between clinical variables. Odds ratios of the multivariate model were used as weights to be applied to each predictor for developing a helpful score to predict SBI. The ROC (receiver operating characteristic) curve was constructed in the plane  $(1-\text{specificity}) \times \text{sensitivity}$  (Figure 1), and the Youden's index was calculated as the optimum cut-off.

Statistical analysis was conducted employing SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

## 3 | RESULTS

From August 2018 to September 2019, 1342 patients were considered eligible; 848 (63%) patients agreed to participate and were enrolled. Forty-eight patients were excluded due to the lack of data at the follow-up (Figure 2). In the end, 800 patients completed the analysis. Table 1 describes the main demographical and clinical

TABLE 1 Descriptive analysis of the main demographical and clinical variables

	Severe infection		p-Value
	No (n = 716)	Yes (n = 84)	
Sex, n (%)			
Female	329 (46.0)	42 (50.0)	0.49 <sup>b</sup>
Male	387 (54.0)	42 (50.0)	
Age (years), median (IQR)	3 (1–5)	3 (1–6)	0.96 <sup>c</sup>
Age class, n (%)			
≤3 years	429 (60.0)	54 (64.3)	0.44 <sup>b</sup>
>3 years	287 (40.1)	30 (35.7)	
Fever in anamnesis ≥ 39.5°C, n (%)			
No	618 (86.4)	64 (76.2)	0.01 <sup>b</sup>
Yes	97 (13.6)	20 (23.8)	
Fever with shivering, n (%)			
No	656 (91.6)	69 (82.1)	0.01 <sup>b</sup>
Yes	60 (8.4)	15 (17.9)	
Gut feeling, n (%)			
No	674 (94.1)	58 (69.0)	<.0001 <sup>b</sup>
Yes	42 (5.9)	26 (31.0)	
Alteration of breathing pattern, n (%)			
No	678 (94.7)	69 (82.1)	<.0001 <sup>b</sup>
Yes	38 (5.3)	15 (17.9)	
Respiratory distress, n (%)			
No	672 (93.9)	73 (86.9)	0.02 <sup>b</sup>
Yes	43 (6.0)	11 (13.1)	
Grunting, n (%)			
No	702 (98.0)	77 (91.7)	0.001 <sup>b</sup>
Yes	14 (2.0)	7 (8.3)	
Child immobility, n (%)			
No	688 (96.1)	75 (89.3)	0.01 <sup>b</sup>
Yes	28 (3.9)	9 (10.7)	
Diarrhoea, n (%)			
No	586 (81.8)	77 (91.7)	0.02 <sup>b</sup>
Yes	130 (18.2)	7 (8.3)	
Parent's concern, n (%)			
No	380 (53.1)	27 (32.1)	0.0003 <sup>b</sup>
Yes	336 (46.9)	57 (67.9)	
Cardiac rate percentiles, n (%)			
<50°	280 (39.1)	31 (36.9)	0.23 <sup>a</sup>
50°–75°	184 (25.7)	20 (23.8)	
75°–90°	111 (15.5)	22 (26.2)	
90°–97°	44 (6.2)	5 (6.0)	
>97°	14 (2.0)	3 (3.6)	

(Continues)

TABLE 1 (Continued)

	Severe infection		p-Value
	No (n = 716)	Yes (n = 84)	
Respiratory rate percentiles, n (%)			
<50°	194 (27.1)	19 (22.6)	0.10 <sup>b</sup>
50°–75°	180 (25.1)	24 (28.6)	
75°–90°	123 (17.2)	14 (16.7)	
90°–97°	70 (9.8)	13 (15.5)	
>97°	35 (4.9)	10 (11.9)	
Symptoms duration (h), median (IQR)	24 (12–48)	42 (24–72)	0.03 <sup>c</sup>

<sup>a</sup>Fisher exact test.<sup>b</sup>Chi-square test.<sup>c</sup>Wilcoxon–Mann–Whitney test.

features of enrolled patients. Four hundred and twenty-eight children were males (53.5%), and 483 were aged <3 years (60.4%) (median age = 3 years, IQR: 1–5 years).

Among the 800 children who entered the final evaluation, 84 (10.5%) were diagnosed with SBI. The most common diagnosis of SBI was pneumonia, followed by pyelonephritis and scarlet fever (see Table 2).

The cardiac frequencies and respiratory rates did not significantly differ among SBI groups. Tables 3 and 4 show the OR, 95% CI, sensitivity, specificity and positive and negative predicted univariate and multivariate logistic regression model values.

In both models, the SBI is more likely to be detected with the 'gut feeling' (univariate OR: 7.16, 95% CI: 4.08–12.56; multivariate OR: 5.34, 95% CI: 2.78–10.25), although the associated sensitivity is low.

The multivariate model misclassifies non-SBI patients rarely. The probability that a child with a negative response to the model will be non-SBI is 0.93. Furthermore, the model will identify a non-SBI child as healthy 86% of the time.

## 4 | DISCUSSION

This study proves that paediatricians' gut feelings and abnormal respiratory patterns are the best predictors to rule out severe bacterial infection in children admitted to the ED. This evidence is explained by the high specificity, which subtends the ability to designate an individual with no SBI as healthy and, therefore, as a child who does not need immediate care. In addition, their high NPV refers to the probability that subjects who do not have an alteration of breathing pattern and do not cause 'gut feeling' in the physician do not have severe disease. The diagnosis of SBI is often challenging, and therefore, different elements available must be analysed,<sup>14</sup> including laboratory tests, image tests, clinical presentation but also the impression that the doctor has of the child who comes to the ED. The prevalence of severe infections between our 800 enrolled patients was 10.5%.

stratifying our setting in the intermediate prevalence (5%–20%). All signs and symptoms were examined individually and chosen to determine whether a child with a severe or nonsevere infection had sensitivity below 70% in the univariate analysis. Specificities in the same research resulted in over 90% for the variables 'gut feeling' and 'abnormal breathing pattern'. A negative predictive value (NPV) was found above 90% for all signs and symptoms selected.

Our study highlighted that gut feeling, taken individually, was the variable which more commonly allowed to rule out an SBI. Previous studies specific to gut feeling investigated the single features independently associated with a worrisome clinical impression<sup>12</sup>: the children's appearance, the pattern of breathing and level of drowsiness were significant, but the trait that was more likely to

provoke a gut feeling resulted from the parental concern, specifically when parents reported that the illness was different from any previously experienced. We tried to separate these characteristics and analyse them individually in this study, but this did not increase the likelihood of finding children at higher risk for SBI. The sign 'gut feeling' was predictive for SBI with high specificity (94%) and NPV (91%). According to previous investigations<sup>12</sup> regarding both in- and out-hospital settings, the 'gut feeling' had high specificity and an elevated positive likelihood ratio for severe infectious illness. The parent concern was predictive for SBI, but due to low specificity, the number of false-positive values was extremely high (53% specificity, 93% NPV). Furthermore, even if more commonly expressed by parents of patients with SBI, parental concern was found to have no value in SBI prognosis in children admitted to the ED.

'Abnormal breathing pattern' was predictive of SBI: this evidence was well known since children with deficiencies in oxygenation or ventilation could present respiratory compromise, as indicated by increased breathing rate and/or effort. Children with respiratory compromise often use accessory muscles to increase tidal volume, resulting in retractions from accessory muscles. Head bobbing and nasal flaring are accessory muscle use and respiratory distress indicators. Moreover, rapid or superficial breathing, grunting, moaning, rejection of favourite toys or activities, inconsolable crying, screaming, irritability, drowsiness, refusal of food or drinks and decreased urination usually were not identified as significant triggers of relatives' concern.<sup>15</sup> Likewise, parental age or level of education was not reported to influence the ability to predict SBI.<sup>15</sup>

As for fever, it is known to account for up to 20%–30% of ED visits,<sup>16</sup> and most children with fever suffer from self-limiting viral

TABLE 2 SBIs aetiologies (n = 84)

	n (%)
Pneumonia	42 (50.0)
Scarlet fever	14 (16.6)
Pyelonephritis	12 (14.2)
Complicated acute otitis media	4 (4.8)
Peritonitis	3 (3.6)
Cellulitis	2 (2.4)
Orbital cellulitis	2 (2.4)
Retropharyngeal abscess	2 (2.4)
Bacteraemia	1 (1.2)
Parotiditis	1 (1.2)
Pleural empyema	1 (1.2)

Variable	OR (95% CI)	p-Value	Se	Sp	NPV	PPV
Gut feeling	7.16 (4.08–12.56)	<0.0001	0.31	0.94	0.92	0.39
Parent concern	2.37 (1.46–3.83)	0.001	0.68	0.53	0.93	0.15
Fever in anamnesis $\geq 39.5^{\circ}\text{C}$	1.99 (1.15–3.44)	0.01	0.24	0.86	0.90	0.17
Absence of diarrhoea	2.47 (1.12–5.49)	0.03	0.61	0.52	0.91	0.14
Abnormal breathing pattern	3.83 (1.98–7.40)	<0.0001	0.18	0.95	0.90	0.29
Child immobility	2.94 (1.34–6.47)	0.01	0.11	0.96	0.9	0.25
Shivering with fever	2.44 (1.31–4.54)	0.01	0.74	0.36	0.92	0.13

Abbreviations: CI, confidence intervals; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

Variable	OR (95% CI)	p-Value	Se	Sp	NPV	PPV
Gut feeling	5.34 (2.78–10.25)	<0.0001	0.48	0.86	0.93	0.30
Parent concern	1.56 (0.92–2.67)	0.10				
Fever in anamnesis $\geq 39.5^{\circ}\text{C}$	2.03 (1.13–3.66)	0.02				
Absence of diarrhoea	2.78 (1.21–6.39)	0.02				
Abnormal breathing pattern	1.79 (0.81–3.96)	0.15				

Abbreviations: CI, confidence intervals; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

TABLE 3 Univariate logistic regression analysis for severe infection, adjusted for age class

TABLE 4 Multivariate logistic regression analysis for severe infection, adjusted for age class

illnesses. However, self-limiting viral illness and SBI presentation may be identical. We observed that the variable 'fever in medical history equal to or above 39.5°C' had a limited value in predicting SBI, with a specificity of 86%, a positive predictive value of 17% and an NPV of 90%. The predictive value of a high temperature reported in the literature was poor: a prospective cohort of nearly 16 000 febrile episodes<sup>17</sup> confirmed the trend towards a higher incidence of serious illness with increasing temperature, but the predictive value remained limited. Remarkably, this concept was firmly age-dependent and did not apply to babies in the first months. Indeed, *Pantell et al.*<sup>18</sup> looked at children of different ages and found a higher predictive value of a body temperature >39°C in infants under 3 months. Additionally, corroborating this evidence, infants under the age of 3 months with temperature higher than 40°C are at increased risk for SBI, while the increased risk of SBI in older children with temperature >40°C is minimal.<sup>19</sup>

Based on these parameters, we attempted to evaluate a possible model. Considering that it had to reach a sensitivity of 90% to be clinically valuable, our model failed, achieving only 48% sensitivity and 87% specificity for our intermediate risk setting.

Previous studies in the ED setting tried to determine whether a flow chart or scale could advise discriminating if ill children would have a positive or negative outcome. A study tried to assess the accuracy and reliability of the Yale Observation Scale (YOS) in febrile children aged 3–36 months for predicting bacteraemia.<sup>20</sup> The YOS was derived from observational parameters, such as cry quality, reaction to parent, state variation, skin colour, hydration and child's response. Children admitted to the paediatric ward with a documented fever of rectal temperature >38°C were enrolled. The results showed that YOS was a reasonably accurate test for predicting bacteraemia, with a high negative predictive value indicating that the scores obtained ruled it out. YOS score and unstructured clinician suspicion were also tested to identify febrile infants ≤60 days old with SBIs presenting to the EDs<sup>21</sup>: neither provided accurate discrimination between infants with either SBIs or invasive bacterial infections and those without SBIs.

Another prior investigation, part of the MOFICHE study (Management and Outcome of Febrile children in Europe),<sup>22</sup> included children aged 0–18 years presenting with fever to the ED in 12 Institutes from eight different European countries and collected data regarding general patient characteristics, vital signs, the presence of alarming signs according to National Institute for Health and Care Excellence (NICE) guideline. The NICE alarming signs included reduced consciousness, ill appearance, increased work of breathing, dehydration, age <3 months, nonblanching rash, meningeal signs, status epilepticus and focal neurological signs. The results were that general patient characteristics, vital signs and NICE alarming signs seemed to be better predictors for children requiring hospital admission than for SBI. Another study analysing a dataset of children between the age of 0 and 16 admitted to outpatient care facilities with acute illness<sup>23</sup> found that only four NICE red features increased the likelihood of SBI. They were: 'does not wake or if roused does not stay awake', 'reduced skin turgor', 'nonblanching rash' and 'focal

neurological signs'. Children with more than one red feature had an increased risk of SBI; however, more than three red features did not further increase disease probability.

#### 4.1 | Strengths and limitations of the study

This study has several limitations. The sample size was limited compared with more extensive series. In terms of methods and data collection, we cannot exclude that some SBIs may have been mislabelled. Moreover, we did not perform routine viral tests, so we cannot exclude that some pneumonia had a viral aetiology. The follow-up was performed by phone and not with a second clinical evaluation. Additionally, the presence of a nonpersistent observer could give rise to a possible Hawthorne effect. Finally, hospital records were not reviewed to ensure that every child was enrolled just once. The strength of this study is the prospective and multicentre design.

## 5 | CONCLUSIONS

This study confirms the importance of the subjective variables in predicting SBI. The signs 'gut feeling' and 'abnormal breathing pattern' were highly relevant in excluding SBI. No other parameter analysed did excel in either sensitivity or specificity: the parents' affirmation that this disease is different from previous conditions was not decisive in deciding whether that child deserved more attention. The lack of specificity in all the analysed variables prevented us from drawing up a helpful model to stratify the risk of severe bacterial infections.

#### ACKNOWLEDGEMENTS

The authors would like to thank Martina Bradaschia for the English revision of the manuscript and Daniele Piccolo for programming the study data collection software. Open Access Funding provided by Università degli Studi di Trieste within the CRUI-CARE Agreement.

#### FUNDING INFORMATION

No specific grant from any funding agency in the public, commercial, or not-for-profit sectors has been received.

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**How to cite this article:** Cozzi G, Tessitore A, Giangreco M, Cogo P, Valentini E, Salis S, et al. SBI is uncommon in the absence of paediatricians' gut feeling and abnormal respiratory pattern. *Acta Paediatr*. 2022;111:2362-2368. <https://doi.org/10.1111/apa.16544>