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PEDIATRIE

par

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Valeur diagnostique d'une approche séquentielle pour stratifier le risque d'infection bactérienne invasive aux urgences pédiatriques, et intérêt potentiel d'une telle approche dans la diminution de l'exposition aux antibiotiques

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I- INTRODUCTION

I-1- Epidémiologie des infections bactériennes aux urgences :

La fièvre est un motif de recours extrêmement fréquent aux urgences pédiatriques. Parmi les enfants de moins de 5 ans consultant aux urgences pour ce motif, la prévalence des infections bactériennes sévères (IBS) se situe selon les études entre 7 et 23%, mais la prévalence des infections bactériennes invasives (IBIs = méningites et bactériémies) est, quant à elle, bien plus basse, entre 0,4 et 1% selon les études (1–3). Le risque d'IBI est néanmoins plus élevé si l'enfant est plus jeune, estimé entre 1,3 et 4,3% avant 3 mois (4–7).

L'instauration des vaccins conjugués antipneumococcique avec le Prévenar 7 puis 13, antiméningococcique et anti-HIB (Haemophilus Influenzae B) ces dernières décennies a permis de faire reculer l'incidence des IBIs (8,9).

I-2 Enjeux du délai d'administration des antibiotiques :

Parmi les IBS diagnostiquées devant une fièvre sans point d'appel, l'infection la plus courante reste la pyélonéphrite. La question du risque de séquelles néphrologiques en cas d'antibiothérapie retardée demeure controversée avec des résultats divergents selon les études. Néanmoins, plusieurs études s'accordent pour dire qu'un délai de 48 heures n'est pas délétère en termes de cicatrices rénales à la scintigraphie. (10–12)

En revanche, une antibiothérapie intraveineuse administrée sans délai est indispensable pour les IBIs. Le lien entre délai d'administration des antibiotiques et mortalité dans le sepsis sévère a notamment bien été démontré chez l'adulte par l'étude de Kumar en 2006 (13).

La crainte des complications en cas d'IBI fait parfois adopter une approche excessive avec une sur-prescription d'antibiothérapies empiriques pour des patients qui s'avèrent finalement

avoir simplement une infection virale bénigne. Ces prescriptions d'antibiotiques en excès contribuent à l'augmentation de l'incidence des résistances bactériennes (14–17). L'inquiétude actuelle se porte principalement sur l'incidence croissante des infections à entérobactéries productrices de bêta-lactamases à spectre élargi (EBLSE) (18), pour lesquelles les prescriptions de céphalosporines de troisième génération effectuent une pression de sélection. Les services d'urgences sont d'importants pourvoyeurs de prescriptions antibiotiques, il est donc nécessaire qu'ils participent au combat commun pour la réduction de l'antibiorésistance en réduisant les antibiothérapies excessives et inutiles.

Par ailleurs, au-delà des effets indésirables sur l'écologie bactérienne de la communauté, les antibiotiques ont un effet néfaste sur le microbiote intestinal de l'individu. Ceci est un sujet de préoccupation notamment chez le jeune enfant, chez qui des perturbations lors de la phase d'installation du microbiote a probablement des effets indésirables à long terme sur le développement de maladies inflammatoires chroniques, d'allergies ou d'obésité (19).

I-3 Aides au diagnostic d'infection bactérienne

Devant une fièvre sans point d'appel clinique évident, l'enjeu est donc de savoir quels seront les rares enfants qui bénéficieront d'une antibiothérapie précoce.

Pour tenter de répondre à cette question, un certain nombre de règles de décision cliniques ou d'algorithmes ont été développés. Ces règles de décision ont des performances diagnostiques variables et ont plusieurs limites :

Tout d'abord, plusieurs règles de décision se basent uniquement sur des paramètres cliniques : le Yale Observation Scale établit un nombre de points en fonction du type de pleurs de l'enfant et de sa réponse aux stimulations, de ses interactions, de la pâleur de sa peau et de son état d'hydratation. Selon le seuil de points déterminé et le lieu d'utilisation de ce score, les performances diagnostiques pour identifier les IBS variaient entre 12 et 46% pour la

sensibilité et entre 81 et 90% pour la spécificité. (20,21) Les recommandations anglo-saxonnes développées par le National Institute for Health and Care Excellence (NICE) comprennent la couleur de la peau (rose, cyanose, pâleur), l'activité et les interactions, la respiration, l'état circulatoire, ainsi que d'autres paramètres (âge, fièvre élevée, purpura, fontanelle bombante, convulsions, raideur de nuque). La sensibilité de cette règle pour l'identification des IBS est relativement correcte entre 82 et 86% mais la spécificité est extrêmement faible, entre 1 et 28% (21,22).

D'autres règles de décision se basent uniquement sur des paramètres biologiques : le « Lab-score » s'établit en fonction du niveau de procalcitonine (PCT), de C-reactive protéine (CRP) et de la présence ou non d'une leucocyturie à la bandelette urinaire. La sensibilité de ce score pour identifier les IBS varient entre 52 et 86% et la spécificité entre 70 et 83%. Les performances de ce sore sont médiocres pour le diagnostic d'IBIs puisque la sensibilité n'était que de 70% (spécificité 84%) dans une étude de 2012 portant sur des enfants fébriles de moins de 3 mois où 7 enfants ayant une IBI aurait été mal « classés » par ce score. (5,23) Ces performances insuffisantes ont conduit les auteurs de ce score à tenter de l'améliorer, en proposant un « refined Labscore », qui prendrait en compte l'âge et le chiffre précis de la CRP et de la PCT. Celui-ci avait une sensibilité de 95% et une spécificité de 87% ce qui semble plus intéressant. Néanmoins la complexité de l'arbre décisionnel et la nécessité d'obtenir un prélèvement sanguin systématique pour tout enfant rend cet outil difficile d'utilisation en pratique quotidienne. (24)

Les règles de décision clinico-biologiques sont probablement les plus intéressantes. Néanmoins, le bilan sanguin est toujours indiqué dans ces règles de décision, ce qui ne correspond pas à la pratique clinique.

Un certain nombre ne s'intéressent uniquement qu'aux enfants de moins de 3 mois : L'arbre diagnostique proposé par Bachur en 2001 classifie ainsi en haut risque les patients présentant une leucocyturie, ou une leucocytose supérieure à 20 000/mm^3 ou inférieure à 4100/mm^3, ou une température supérieure à 39,6°C, ou un âge inférieur à 13 jours. Les performances de cet

arbre semblent intéressantes avec une valeur prédictive négative de 98,3% (IC 95% 97,8-98,7) pour éliminer une IBS et de 99,6% (IC 95% 99,4-99,8) pour éliminer une IBI. (4) Dans le même esprit, un arbre diagnostique appelé « Step-by-step » a été proposé par Mintegi plus récemment, classant selon 3 niveaux de risque en fonction de l'apparence toxique, de l'âge (seuil à 21 jours), de la leucocyturie, des dosages sanguins de la PCT (≥0,5 ng/ml), de la CRP (≥20 mg/L) et des polynucléaires neutrophiles (≥ 10 000/mm^3). (25) L'étude de validation de cette approche retrouvait une sensibilité à 92% (IC 95% 84,3 – 96,0) avec une VPN à 99,3% (IC 95% 98,5 – 99,7) pour la détection des IBIs, ce qui semble intéressant, néanmoins 7 enfants avec une IBI étaient « mal classés » dans le groupe bas-risque (6). Très récemment, une équipe américaine a publié une étude en dérivant puis validant une règle de décision sur une population d'enfants de moins de 2 mois. Ces enfants étaient considérés à bas risque s'ils avaient une bandelette urinaire négative, un chiffre de polynucléaires ≤ 4090/mm^3 et une PCT ≤ 1,71 ng/mL. La sensibilité dans la population de validation était de 99,7% (IC95% 91,3-99,6) et la spécificité 60% (IC95% 56,6-53,3). Ceci résultait néanmoins en la mauvaise classification de 3 IBS dont 1 IBI. (26)

Une autre approche développée est celle d'un modèle clinico-biologique prédictif, qui en fonction d'un certain nombre de paramètres intégrés à une application ou un logiciel informatique en tire un pourcentage de risque d'infection bactérienne. Cette approche a été développée par Nijman (avec comme paramètres : âge, durée de la fièvre, température, temps de recoloration cutané, fréquence cardiaque, fréquence respiratoire, apparence septique, signes de lutte respiratoire, saturation en oxygène, CRP) puis améliorée par Irwin en 2017 (variables refittées et ajout de la PCT et de la résistine dans les paramètres). Les performances diagnostiques de ce modèle dépendent du seuil à partir duquel on considère le risque d'IBS : pour un seuil de 2,5% on obtient une grande sensibilité 97% (IC95% 94-99) mais une faible spécificité 18% (IC95% 15-20), inversement pour un seuil de 30% on obtient une faible sensibilité 53% (IC95% 45-61) mais une assez bonne spécificité 94% (IC95% 92-95) (27,28).

I-4 Etudes d'impact des règles de décision :

Très peu d'études d'impact ont été publiées à propos de toutes ces règles de décision et algorithmes. Une étude de 2014 avait comparé de façon randomisée une prise en charge « classique » versus une prise en charge selon le « Labscore » et ne retrouvait pas de différence significative en ce qui concernait les prescriptions d'antibiotiques (29). Une autre étude en 2015 comparait une prise en charge « classique » à une prise en charge guidée par un logiciel donnant un pourcentage de risque d'IBS et de pneumopathie, et proposant une prise en charge selon l'algorithme de Nijman. Aucune différence n'était retrouvée en termes de diagnostic correct, ni de temps de passage aux urgences, ni de taux de prescription antibiotiques (30).

I-5 Etude pré-DIPI :

Dans ce contexte, nous avons construit un algorithme séquentiel permettant de stratifier le risque d'IBI chez des enfants de moins de 5 ans se présentant aux urgences pédiatriques pour une fièvre sans point d'appel, en prenant en compte l'apparence toxique de l'enfant, son âge, la leucocyturie et la valeur de la PCT. L'objectif principal de cette étude était d'étudier les performances diagnostiques de cette approche. L'objectif secondaire était d'étudier la potentielle diminution du taux de prescriptions d'antibiotiques que cette approche permettrait.

Nous présentons dans cette thèse les résultats de ce travail sous forme d'article scientifique rédigé en anglais.

II- ARTICLE

II-1 Title page:

TITLE: Diagnostic value of a new sequential approach to identify young febrile infants at low risk for invasive bacterial infection and potential impact to decrease antibiotic exposure in emergency departments.

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II-2 Abstract (234 words):

Objective: The first objective was to assess the value of a sequential approach to identify patients at a low and intermediate risk of invasive bacterial infections (IBI) among febrile infants. The secondary objective was to assess the utility of such an approach to decrease antibiotics exposure comparing with actual observed practices.

Design, settings and population: We conducted a prospective study including all infants ≤ 5 years presenting in one French pediatric Emergency department with fever without source (FWS) between January and December 2016. We constructed a sequential algorithm using multinomial logistic model, based on age, clinical toxic signs, urine analysis and procalcitonin.

Main outcome measures: We calculated sensitivity, specificity, predictive values and post-test probabilities of the sequential approach to detect IBI (defined as isolation of a bacterial pathogen from the blood or cerebrospinal fluid).

Results: Among the 1061 infants included (IBI 11/1061 1.04%), 693 (65.3%) were classified with a low or intermediate risk, with a IBI prevalence of 0% [95% CI 0-0.6]. The sensitivity and specificity of this approach to predict IBI were 100% [95% CI 71.5-100] and 73.9% [95% CI 70.9-76.7]. Observed antibiotics exposure was 33.6%. Using this new algorithm, we would reduce this antibiotic exposure to 24.1%, corresponding to 9.5% of absolute decrease and 28.3% of relative decrease. The net reclassification improvement was 8%.

Conclusion: This sequential approach showed good accuracy to detect IBI, with a potential interest in decreasing antibiotics exposure.

Keywords: fever without source, invasive bacterial infections, serious bacterial infections, Procalcitonin, antimicrobial prescription

Key points

What's known on this subject?

- Fever is one of the most common reason for consulting in pediatric emergency department.

- A little number of these children will suffer from invasive bacterial infection, for whom diagnostic delay can be severe.

- Over prescription of antibiotics leads to development of bacterial resistance, microbiota disturbance, and its long-term adverse consequences on health.

What this study adds?

- We constructed a sequential approach, for children aged less than 5 years, based on age, simple clinical variables, and if indicated laboratory parameters including procalcitonin

- This approach can identify a group of febrile infants with very low-risk of IBI that can be safely managed without antimicrobial with a sensitivity 100% [95% CI 71.5-100] and a specificity 73.9% [95% CI 70.9-76.7]

- Using this approach may be useful to reduce unnecessary antibiotic treatments.

II-3 Introduction:

Fever is one of the most common reasons for infants to present to pediatric emergency department (PED). Fever may be challenging in young infants when not accompanied by specific symptoms guiding to the diagnosis. Although the majority of children with fever without source will have a self-limited viral illness, 7-23% of febrile children < 5 years admitted in PED suffer from serious bacterial infections (SBI) (1–3). Among SBI, pyelonephritis is the most common infection. If a 48h delayed antibiotic treatment (ATB) is not deleterious for pyelonephritis in absence of sepsis signs (10,11), however, there is an imperative for quickly and accurately detecting the two invasive bacterial infections (IBI) : bacteremia and bacterial meningitis, for which an early recognition and adequate treatment are necessary to avoid complications or death (13,31). Consequently, despite the decreased incidence of IBI since the introduction of conjugate vaccines (8,9), physicians still adopt a minimum-risk approach to children with febrile illness and often prescribe empirical ATB for *a posteriori* self-limiting infections, which contributes to increase ATB resistance (14–17).

Clinical prediction rules (CPR) have the potential to improve diagnostic decision making for rare but serious pathologies. However, previously published CPRs (4–6,20,22,24,27,28,32) focused only on clinical parameters (20,22) or only on laboratory parameters (4,5,24) when other approaches combining clinical and laboratory data are difficult to use in current practice because requiring systematic blood sample investigation (6,27,28,32). Moreover, the published regression models that provide a post-test probability of infection do not fit with usual clinicians' process of treatment decisions (27,28) and seemed to have few impact on ATB rates and discharge from ED

(29,30). Thus, the appropriate approach to the diagnostic evaluation of febrile infants is still an area of clinical debate.

In this context, we constructed a sequential algorithm for IBI risk stratification taking into account the children's ill appearance, age, urine dipstick and PCT value which is known to be a more suitable biomarker than CRP in IBI diagnosis, especially in very early-onset fever (3,33). The aim of the study was to assess the diagnostic value of this algorithm in identifying febrile infants with intermediate and low risk of invasive bacterial infection. The secondary objective was to show a potential decrease in ATB exposure comparing to current practices.

II-4 Methods

Study design and setting

We conducted an observational prospective study in a French pediatric emergency department (PED) from January 1 to December 31, 2016. The participants and their parents received oral and written information. Parents were also informed on the study design on billboards located in the PED. The Ethics Committee for Health in Nantes approved the study design. We applied TRIPOD reporting guidelines for prediction model development and validation studies.

Inclusion and exclusion criteria

We consecutively recruited all children who were older than six days and younger than five years of age, presenting with FWS ≥38°C at home and/or at the PED, measured in a suitable way with axillary or rectal temperature. Patients were excluded when the temperature was not measured or was below 38°C, when the medical history or the physical examination found the origin of the fever, or when the parents refused to participate.

Data collection and management of the patients

The following data were recorded for the included patients: demographic (age, sex), duration of fever, medical history, clinical “toxic signs”, results of laboratory test, diagnosis, treatment, site of care, and follow-up.

After clinical medical examination, physicians were free to prescribe complementary tests or no: Urinalysis, white blood cell (WBC), absolute neutrophil cell

(ANC), C-reactive protein (CRP), procalcitonin (PCT) measurements, chest radiography, lumbar puncture. The decision to treat with antibiotics or to hospitalize was at the discretion of the physicians.

Admitted children received follow-up care throughout the duration of their hospitalisation. Discharged children received a follow-up 8 days after the initial admission by means of a telephone call. After three failed attempts to connect by telephone, clinical courses were reported as being favourable if the child did not re-visit the PED or medical wards of the hospital, according to the electronic registry of the PED.

Definitions

- FWS: Temperature measured at home or at the PED ≥ 38°C in a suitable way (i.e. axillary or rectal temperature), in patients with a normal physical examination and no respiratory signs/symptoms or a diarrheal process.
- “Toxic” symptoms/signs were the following: ILL (irritability, lethargy, low capillary refill)-appearance, tachypnoea, cyanosis, bulging fontanelle, serious concerns by the parent(s) and/or clinician, fever greater than 40 degrees, and purpura, at home or at PED. (34)
- A life-threatening appearance at admission was defined as a hemodynamic failure requiring IV fluid bolus, a respiratory failure requiring oxygen therapy and/or neurological failure defined as a decreased level of consciousness at admission. These signs of gravity were systematically accompanied by toxic signs. (35)

- IBI was defined as the isolation of a pathogenic bacterium from the blood or cerebrospinal fluid (CSF). *Staphylococcus epidermidis* and *Streptococcus viridans* were considered to be non-pathogenic in the study population.
- Non-IBI was defined as the isolation of a pathogenic bacterium from urine with leucocyturia ≥ 10/mm^3 and a positive urine culture defined by the growth of ≥ 10 000 CFU/mL (6)
- SBI was defined as the presence of a non-IBI and/or an IBI
- In case of a strong suspicion of bacterial infection with no positive bacterial culture, the case was discussed among the principal investigators so as to assign the child to the appropriate risk group.

Sample analysis

Urine samples for culture were collected by urethral catheterization for incontinent children and by mid-stream for continent children.

Serum PCT was determined in single measurement with BRAHMS PCT Sensitive assay with a Kryptor Compact Plus instrument - Thermo Fischer Scientific - B.R.AH.M.S (Hennigsdorf, Germany).

Construction of the risk stratification and performance of the CDR

To identify variables associated with a risk of IBI and SBI we performed univariate analysis and then multivariate analysis. Candidate variables were those already described in the literature: toxic signs, life threatening event, age (in class 0-1; 1 to 3 and more than 3 months), past medical history of uropathy, duration of fever,

leucocyturia and PCT. We defined PCT cut off for IBI for each age range with ROC curve as the best compromise between sensitivity and specificity with a higher consideration for sensitivity given the potential severity of IBI. This cut-off was different for children less than 3 month (0.5 ng/mL) and children older than 3 months (1 ng/mL). We constructed a multinomial logistic model for all the population (Table S1, online appendix) to take into account three outcomes: no bacterial infection, IBI and SBI. To avoid overfitting due to the small number of IBI we estimated the coefficient of logistic regression through jackknife method. To construct these CPR we hierarchized the variables as in clinical situation: age class first, then toxic signs, then anamnestic data for children older than 3 months (past medical history of uropathy, duration of fever), then complementary test results: leucocyturia and PCT. Final decision trees with all the included children are described in Figures 3a-c . We also derived the decision tree while partitioning the population in 2/3 (N=795) vs 1/3 (N=266), these trees with their performances are presented in online appendix. According to our clinical experience and literature data, we chose to introduce an intermediate risk, even if there was none SBI neither IBI in this subgroup because a lot of infants consulted early after the beginning of fever making inflammatory markers falsely negatives and because of our little effective of IBI.

Sensitivity, specificity, negative and positive predictive values and likelihood ratio values for IBI and SBI were calculated to assess the new prediction rule. We also assessed the performance of the decision tree with the net reclassification improvement (NRI). When the new tested model changes the classification of a child with an actual IBI from the status “no suspicion of IBI” to “suspicion of IBI” then the new model is considered as improving the classification. On the contrary, when the model changes the status of a children with an actual IBI from “suspicion of IBI” to “no

suspicion of IBI" then it is considered to worsen the classification. An inverse interpretation is made for child without the actual outcome (not infected). The NRI is the sum of differences of the rate of children with an actual IBI up-warded minus the rate of those down-warded, and the rate of children without IBI down-warded minus the rate of those up-warded.

The statistical analyses were performed using STATA statistical software. Statistical significance was defined as *p-value* < 0.05. Our study was observational, based on a cohort previously published which had determined our sample size. Patients who did not had all samples provided for in the CPR were classed as missing data and were not included in the analysis.

Proposed strategies depending on the risk stratification and impact on antibiotic and tests prescription

The sequential algorithm was considered "positive" when the children were classified as high-risk, and "negative" when classified as intermediate and low-risk. For children classified as high-risk, we would propose to quickly begin ATB, those classified as intermediate would be under hospital surveillance without immediate ATB and those classified as low-risk would be discharged home without ATB.

The potential impact of the new CPR was estimated when considering these management propositions versus the really observed practices of ATB prescriptions in this population.

We calculated the absolute difference of antibiotic prescription rate as well as the relative reduction.

II-5 Results

Patients' characteristics, clinical and management data

Overall, 35 561 children attended in the PED between January and December 2016, including 1061 infants ≤ 5 year-old with FWS. (Figure 1). Three hundred and fifty-six infants (33.6%; CI 95% 30.8-36.4) received empiric antibiotic therapy including 300 who received intravenous third generation cephalosporin, and 194 (18.3%, CI95% 16.0-20.6) hospitalised. While 47.4% (CI95% 34.9-60.2) of the infants aged under 1 month were admitted in the ED less than 6 hours after the beginning of fever, only 15.2% (CI95% 12.7-17.7) of the infants older than 3 months were admitted in this early timing. Urine dipstick was performed for 704 infants (66.4%, CI95% 63.6-69.2), urine culture for 431 (40.7%, CI 95% 37.7-40.7) and blood tests for 681 (64.2%, CI95% 61.3-67.1).

Of the 1061 included infants, 125 were diagnosed with an SBI (11.8% CI 95% 9.9-13.7), including 11 with an IBI (1% CI95% 0.4-1.7) (Table 1). ATB exposure was 356/1061 (33.6%; CI 95% 30.8-36.4).

Prevalence of bacterial infections and rate of exams and antibiotic prescriptions varied with the infant age: 7.1 % IBI (CI95% 2.8-16.9), 100% (CI95% 93.6-100) hospitalization and 94.6% (CI95% 85.3-98.1) of antibiotic prescription before 1 month of age versus 0.5% IBI (CI95% 0.1-0.9), 9.4% hospitalization (CI95% 7.6-11.2) and 29.1% of antibiotic treatment (CI95% 26.4-31.8) after 3 months of age. We observed a steady decline in the prevalence of IBI as age was advanced. (Figure 2)

Among the 11 infants with IBIs, 4 (36.4%) have an *Escherichia coli* infections (including 3 UTI with bacteraemia), 3 (27.3%) a group B streptococcal infection (including 1 meningitis), 1 meninogococcal C meningitis occurring in an unvaccinated infant, 1

pneumococcal endocarditis in a previously vaccinated infant of 10 months of age, 1 extremely severe infection due to *Streptoccus pyogenes* and leading to death, and 1 aseptic purulent meningitis. Characteristics of the IBIs are detailed in supplemental appendix (Table S2 online appendix). Among the UTIs, 3/114 (2.6% CI95% 0.3-5.5) were caused by Enterobacteriacae resistant to cephalosporins.

Diagnostic accuracy of the algorithm

Applying our algorithm, the prevalence of IBI and SBI in the different subgroups are shown in figures 3a-c and the diagnostic accuracy measures are shown in tables 2a-b. The algorithm had a negative predictive value for IBI of 100%, a sensitivity of 100% (CI95% 71.5-100), a negative post-test probability of 0 (CI95% 0-1) and a positive post-test probability of 4% (CI95% 4-5). The NRI for IBI was 8%.

Among the 256 high-risk patients, there were 11 IBI (4.3% CI95% 1.8-6.8) and 107 SBI (41.8% CI95% 35.8-47.8) versus 0 IBI (0% CI95% 0-0.6) and 17 SBI (2.5% CI95% 1.6-4) among 693 intermediate and low risk patients, ($p<0,001$ for both IBI and SBI). Children diagnosed with a SBI who were misclassified as low-risk patients were all aged more than 3 month with no toxic sign, recent fever <48h and no history of UTI or urogenital disease.

In age classe > 3 months, the variable “PCT > 1 ng/mL” permitted to detect 2/4 patients with IBI.

Potential decrease of antibiotic prescription

Applying our algorithm, children were classified as following: 256 (24.1% CI95% 21.5-26.7) high-risk patients, 105 (9.9% CI95% 8.1-11.7) intermediate-risk patients, and 588 (55.4% CI95% 52.4-58.4) low-risk patients. There were 112 (10.6% CI95% 8.7-12.5) non-classable patients, due to missing data. When testing the new CPR risk

stratification management, we could limit the antibiotic treatment to 256 febrile children only (24.1% CI95% 21.5-26.7), versus 356 observed ATB prescriptions (33.6%; CI95% 30.8-36.4), resulting in a 28.3% relative decreased exposure and a 9.5% absolute decreased.

II-6 Discussion

Key results and internal validity

With this algorithm based on routine clinical data and simple biological tests, we were able to accurately classify all the IBIs in a high-risk group, while potentially reducing ATB exposure.

Among the few items combined in our algorithm, the first was the age. Most classic studies consider 3 months old as the cut-off under which a sepsis workup including biological samples is recommended. (5,6,34) As suggested in most studies, (34,36,37) our results show that the younger the infant was the higher the IBIs rate was, which suggested us to manage more carefully young infants less than 28 days-old. The second item was the clinical toxic signs which have been previously described as being predictors of SBI. (1,38) Leukocyturia identifies infants at high risk of having a UTI with a strong OR in almost all subgroups. In the sub-group of infant > 3 months of age with toxics signs, it was also associated significantly with an increased risk of IBI because UTI associated with bacteraemia is a frequent cause of IBI in young children. (39) Lastly, many studies reported the interest of PCT value in the management of young febrile infants with better diagnostic value than CRP or WBC to rule in an IBI. (2,3,7,33,40–42) Its rapid kinetic is especially interesting in young infants who, for a large majority, present to the PED with a very early onset fever. (2,7,40) In our study, low PCT value is able to identify low risk patient among those aged more than 3 months old who had toxics signs and no leukocyturia, showing the interest of this biomarker in this subgroup. Moreover, we found that the optimal cut-off points for the identification of IBI in children were lower in infants younger than 3 months comparing with those aged 3 to 60 months. (2)

While 100% of patients with IBI are classified as high-risk infants, only 85,6% of SBI patients were identified as high-risk infants. All the misclassified SBI had a beginning UTI, diagnosed at a second emergency consultation. However, the impact of an early treatment of acute UTI in infants and young children on the incidence of severe sepsis and renal squarring is still an area of debate (10,11) and the benefit of systematically performing a urine sample in all children with recent FWS <48 hours seems limited. However, the clinician must ensure that the parents will consult again in case of persistent fever.

Interpretation and external validity

Our study has some limitations. First, the prevalence (pre test probability) of IBI and SBI varied commonly among publications, and constitute a potential bias when comparing the diagnostic values of various markers and CPR in febrile infants. Concerning infants aged more than 3 months, we found a lower prevalence of SBI than Andreola (3) possibly explained by the fact that they included only infants blood sampled, and a higher prevalence than Craig (1) explained by the fact that they included all febrile infants and not only those with FWS. Secondly, the observed reduction rate of antibiotic exposure is related to our local usual prescription rate. However, in recent European data from the PERFORM study, the median prescription rate of ATB was also 32% (43). Finally, due to the small number of IBI, our model may be overfitted. To minimize this risk, we used jacknife method for the preliminary regression logistic model and tested the algorithm on 2 randomly samples (2/3 and 1/3) of our study population and showed good performances in these populations. This algorithm has now to be validated on a multicentric study.

Implications for practice

It is highly important to reduce excessive exposure to antibiotics in young infants. Approximately 700 000 deaths per year worldwide are attributable to antibiotic resistance (17). The relation between antibiotic selective pressure and the emergence of antimicrobial resistance has been demonstrated (15) and antibiotic resistance can be reversed by reducing the inappropriate use of antibiotic (15–17). Moreover, prolonged antibiotic exposure, specifically in the early life period has been associated with changes in the microbiome, which could affect long-term health (19).

II-7 Conclusion

In this population of young infants consulting for FWS in the ED, this new sequential approach to identify those at low risk for serious bacterial infection demonstrates good diagnostic performances, with a specifically good negative predictive value to exclude IBI and would result in a potential reduce of 28,3% of the ATB prescription. The next step will be to integrate a procalcitonin point-of-care rapid test in the algorithm, in order to limit also the painfulness of venipuncture and the length of stay in ED before conducting a study validation in additional multicentric population.

II-8 Figures

Figure 1. Flow chart

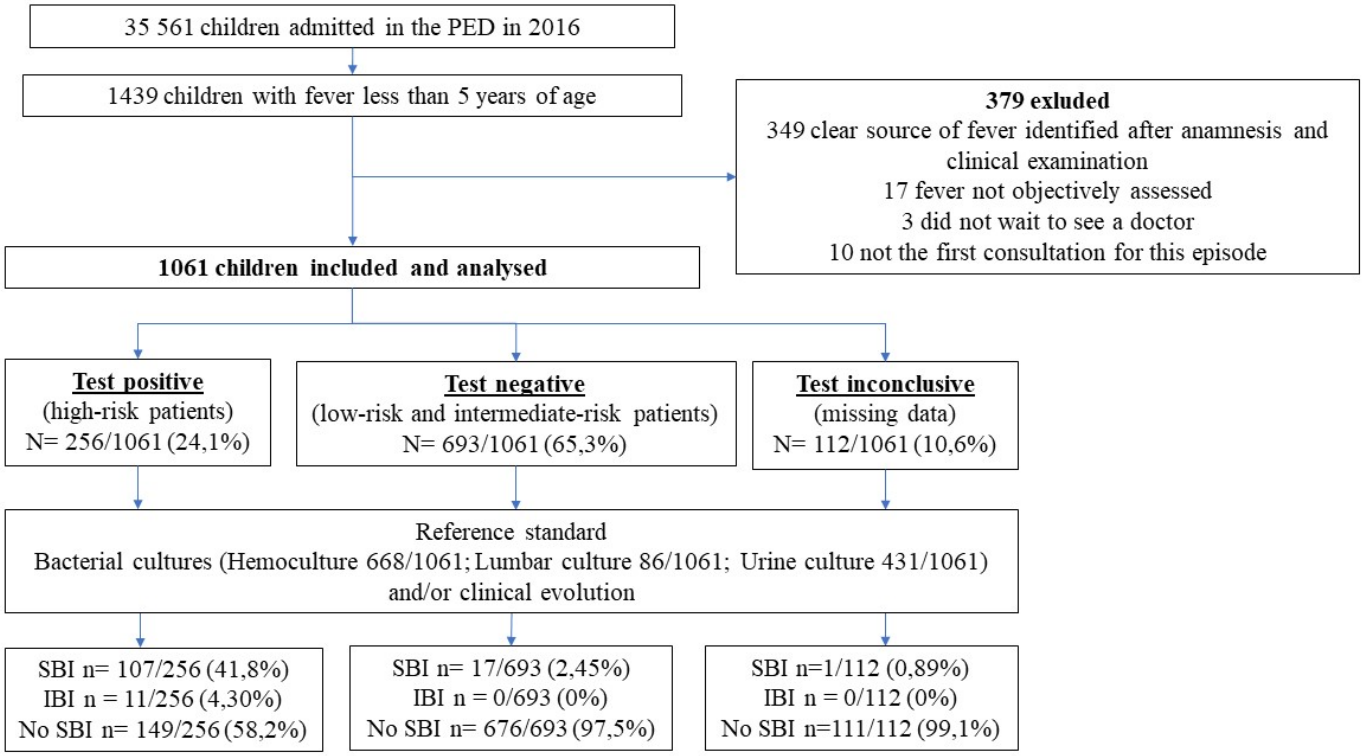


Figure 2. Proportion of IBI and SBI with CI95% according to age

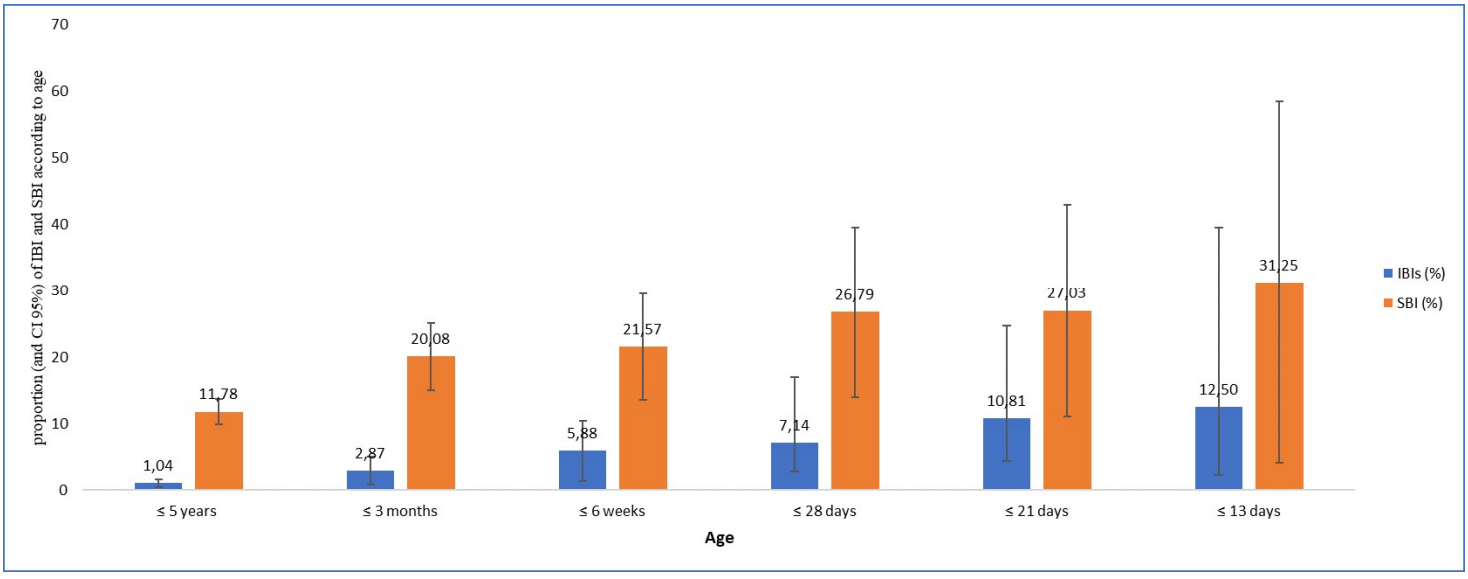


Figure 3a. Prevalence of SBI and IBI in 56 infants aged 6 days - 1 month in the different risk subgroups and OR with 95% CI for those infants presenting each risk factor.

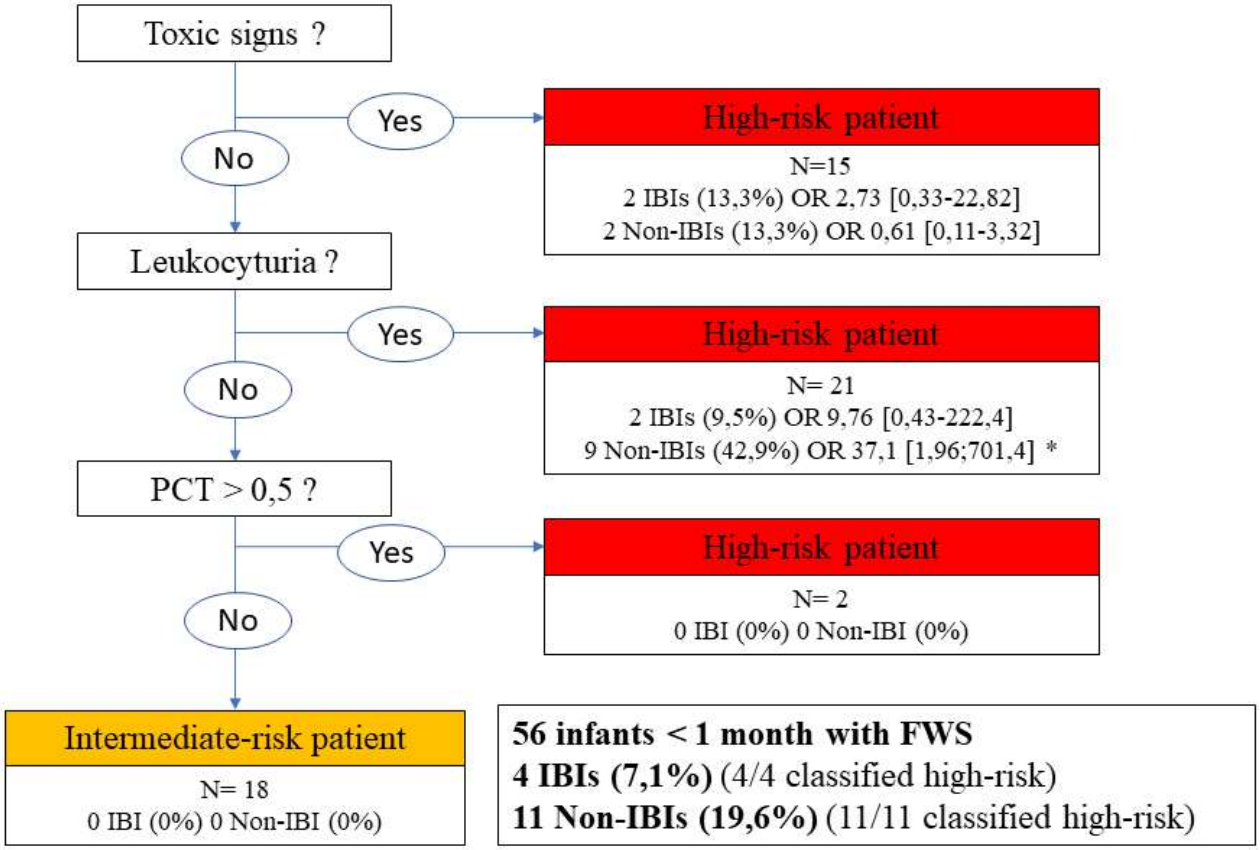


Figure 3b. Prevalence of SBI and IBI in 188 infants aged 1 - 3 month in the different risk subgroups and OR with 95% CI for those infants presenting each risk factor.

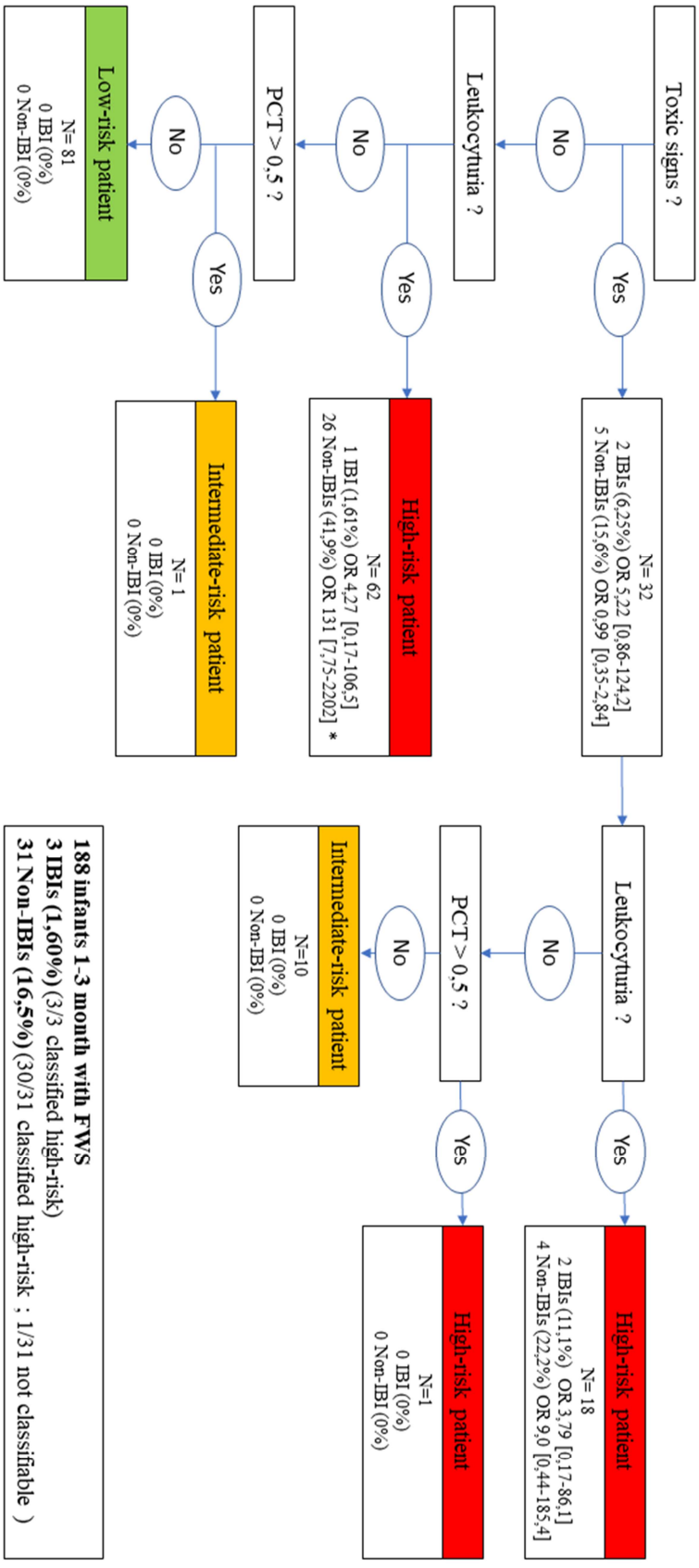
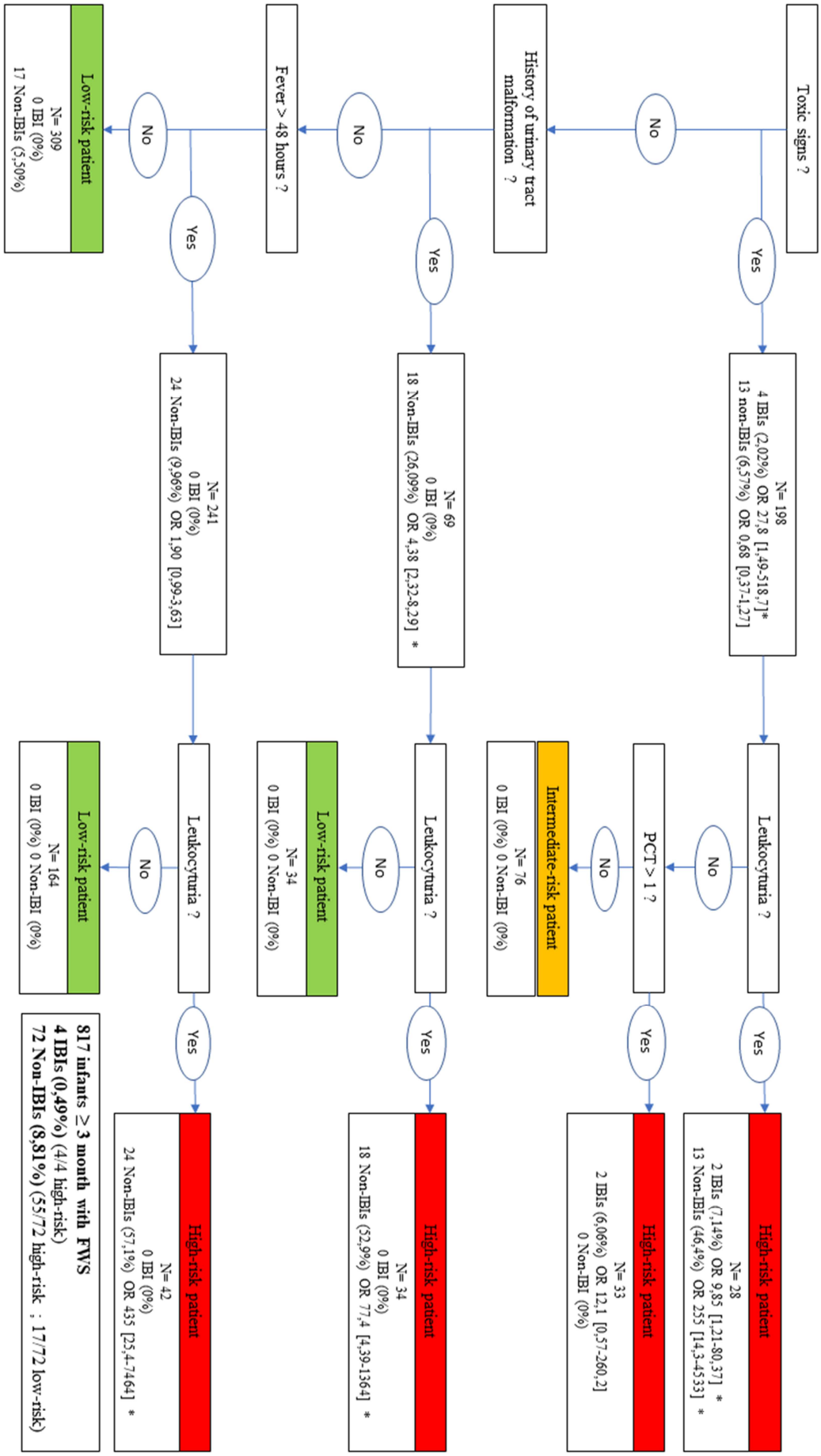


Figure 3c. Prevalence of SBI and IBI in 816 infants aged > 3 months in the different risk subgroups and OR with 95% CI for those infants presenting each risk factor.



III-9 Tableaux

TABLE 1: Proportion of bacterial infections according to age: No. (%) of patients

	Total N=1061	**≤ 1month n=56**	**1-3 months n=188**	**> 3 months n=817**
Serious Bacterial infections	125 (11,78)	15 (26,79)	34 (18,08)	76 (9,30)
Invasive Bacterial Infections	11 (1,04)	4 (7,14)	3 (1,60)	4 (0,49)
Meningitis (2)	5 (0,47)	3 (5,36)	1 (0,53)	1 (0,12)
Bacteremia (3)	10 (0,94)	4 (7,14)	2 (1,06)	4 (0,49)
UTI with bacteremia	3 (0,28)	1 (1,79)	1 (0,53)	1 (0,12)
Meningitis with bacteremia	3 (0,28)	2 (3,57)	0 (0)	1 (0,12)

Legend

1 : UTI associated with bacteremia are not included

2 : meningitis associated with bacteremia are included

3 : isolated bacteremia or associated with meningitis or UTI are included

TABLE 2a Diagnostic performances with 95% CI, of the approach for identifying IBIs

	Total	≤ 1 month	1-3 month	>3 months
Prevalence of IBI (%)	**1,04**	**7,14**	**1,60**	**0,49**
Sensitivity (%)	100 [71,5-100]	100 [39,8-100]	100 [29,2-100]	100 [39,8-100]
Specificity (%)	73,9 [70,9-76,7]	34,6 [21,9-49,1]	54,1 [46,3-61,8]	81,4 [78,4-84,2]
Positive Likelihood Ratio	3,83 [3,44-4,26]	1,53 [1,25-1,86]	2,18 [1,85-2,57]	5,38 [4,62-6,28]
Negative Likelihood Ratio	0 [-]	0 [-]	0 [-]	0 [-]
Positive Predictive Value (%)	4,30 [3,88-4,76]	10,5 [8,80-12,5]	3,70 [3,16-4,33]	2,92 [2,52-3,39]
Negative Predictive Value (%)	100 [-]	100 [-]	100 [-]	100 [-]

TABLE 2b Diagnostic performances with 95% CI, of the approach for identifying SBIs

	Total	≤ 1 month	1-3 month	>3 months
Prevalence of SBI (%)	**11.78**	**26.79**	**18.08**	**9.30**
Sensitivity, %	86,3 [79,0-91,8]	100 [78,2-100]	100 [89,4-100]	77,6 [66,6-86,4]
Specificity %	81,9 [79,1-84,5]	43,9 [28,5-60,3]	65,7 [57,2-73,5]	87,9 [85,1-90,3]
Positive Likelihood Ratio	4,78 [4,07-5,61]	1,78 [1,36-2,34]	2,92 [2,32-3,67]	6,41 [5,04-8,15]
Negative Likelihood Ratio	0,17 [0,11-0,26]	0 [-]	0 [-]	0,25 [0,17-0,39]
Positive Predictive Value, %	41,8 [37,9-45,8]	39,5 [33,2-46,1]	40,7 [35,3-46,4]	43,1 [37,3-49,0]
Negative Predictive Value, %	97,6 [96,2-98,4]	100 [-]	100 [-]	97,1 [95,6-98,1]

II- 10 Supplemental appendix

Figure S1a. sequential algorithm for infants aged less than 1 month in group 1 (derivation population)

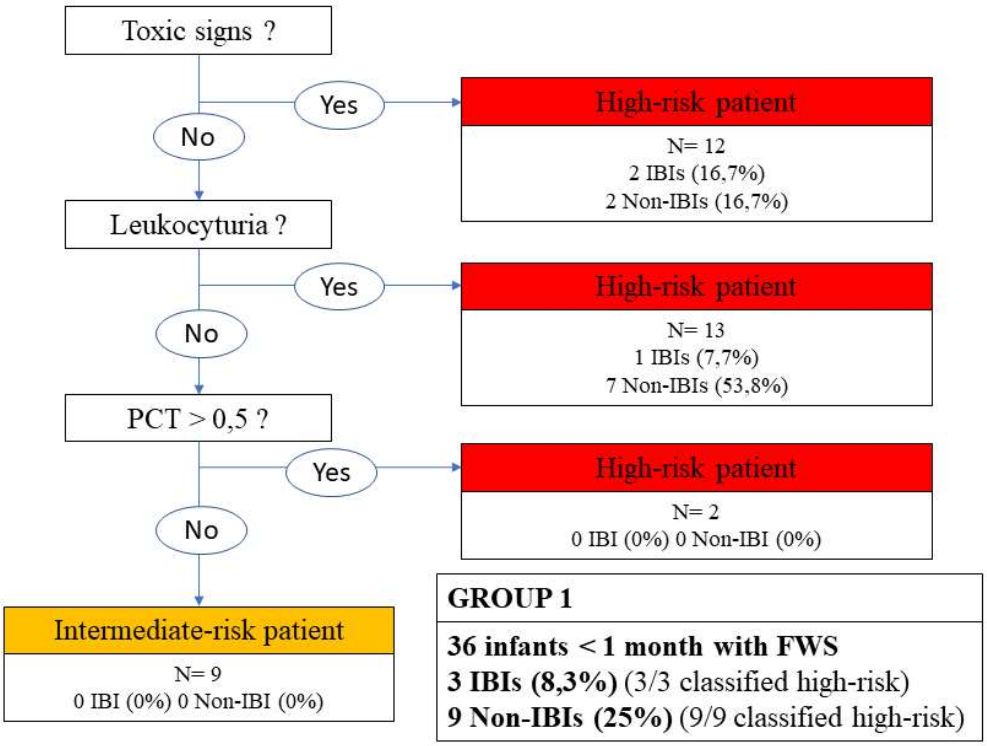


Fig S1b. sequential algorithm for infants aged 1-3 month in group 1 (derivation population)

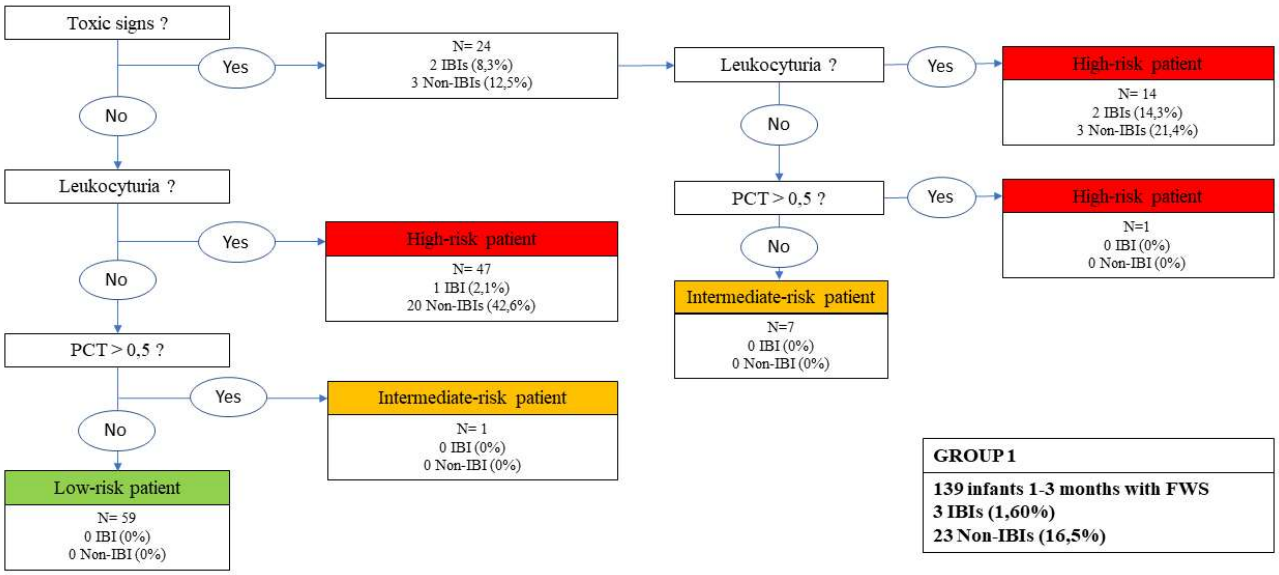


Fig S1c. sequential algorithm for infants aged more than 3 month in group 1 (derivation population)

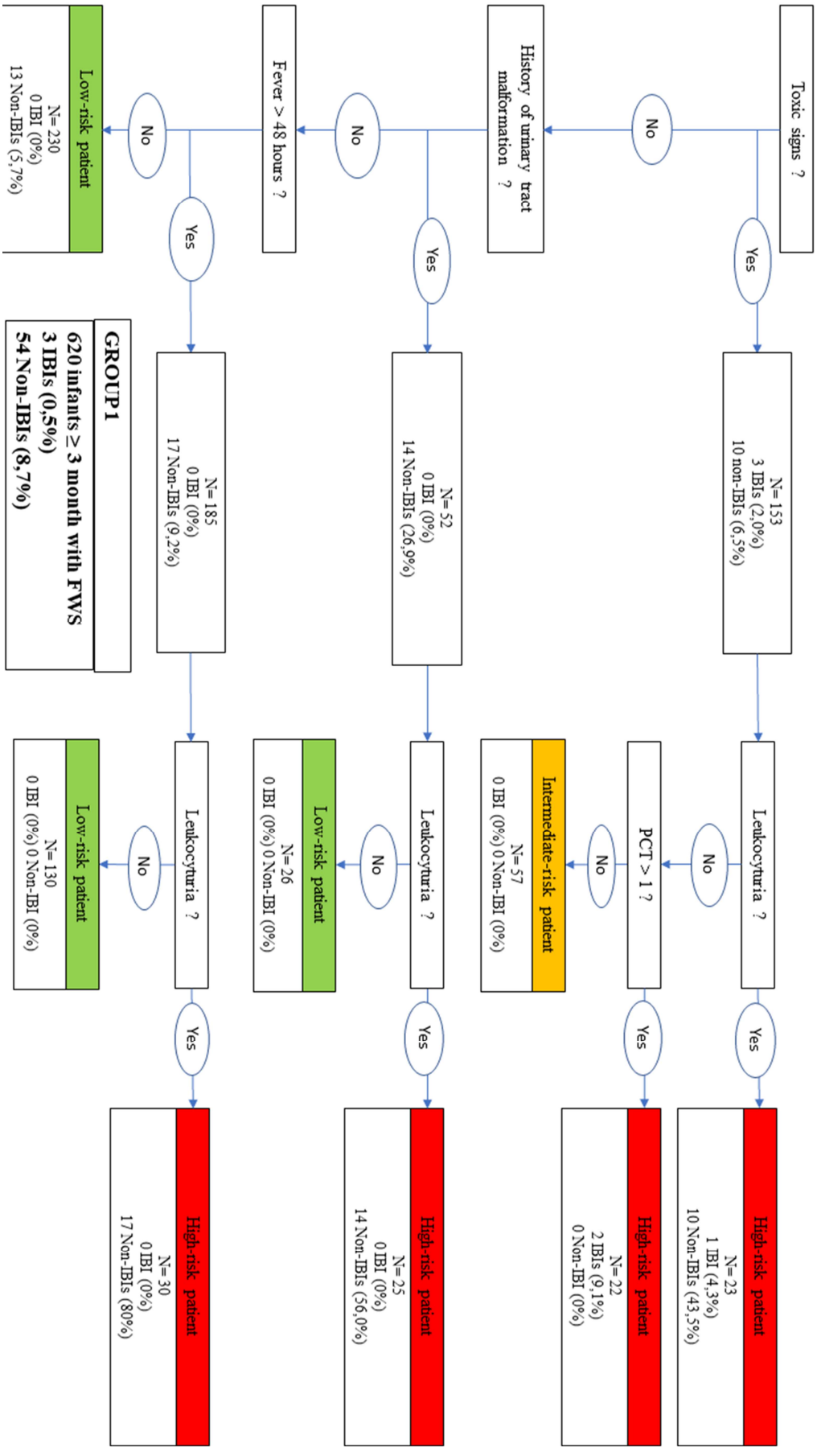


Fig S2a. sequential algorithm for infants aged less than 1 month in group 2 (validation population)

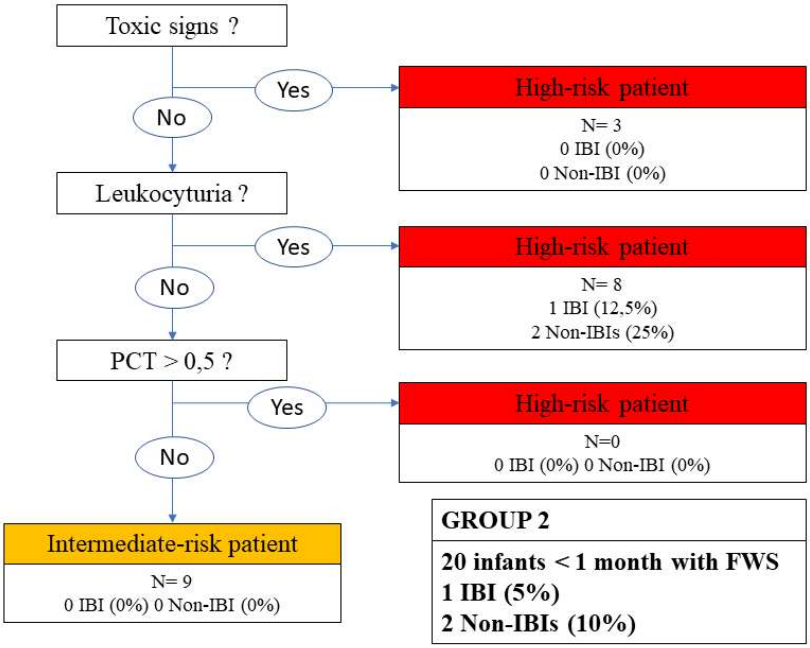


Fig S2b. sequential algorithm for infants aged 1-3 month in group 2 (validation population)

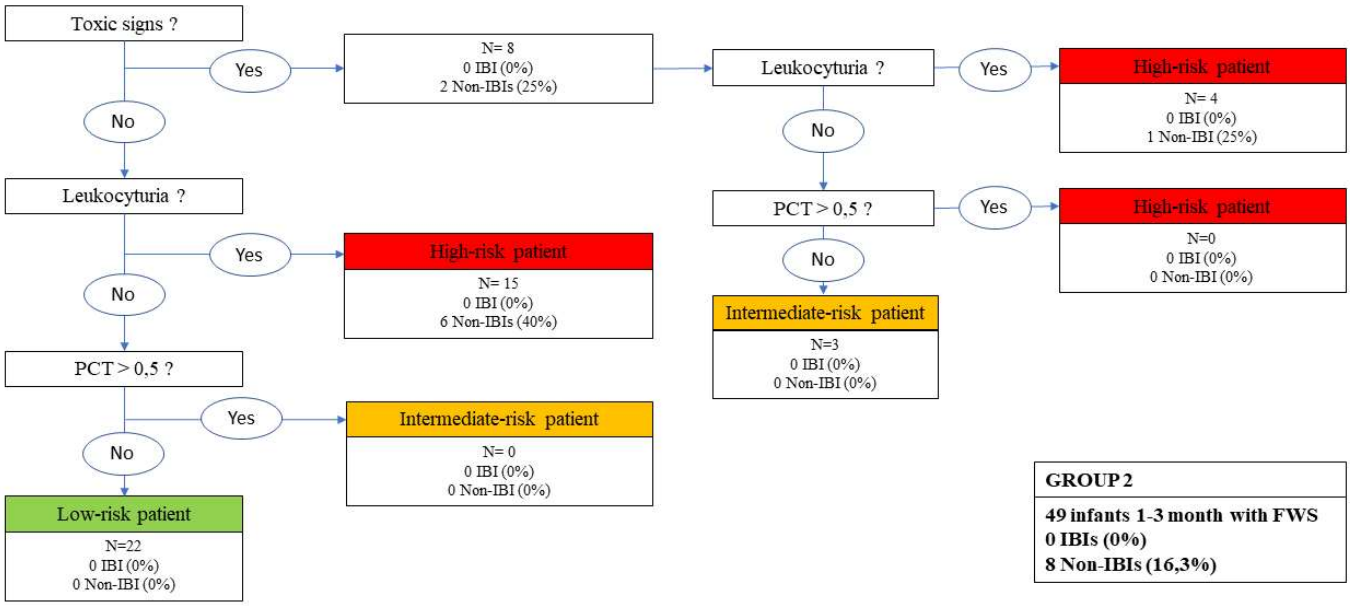


Fig S2c. sequential algorithm for infants aged more than 3 month in group 2 (validation population)

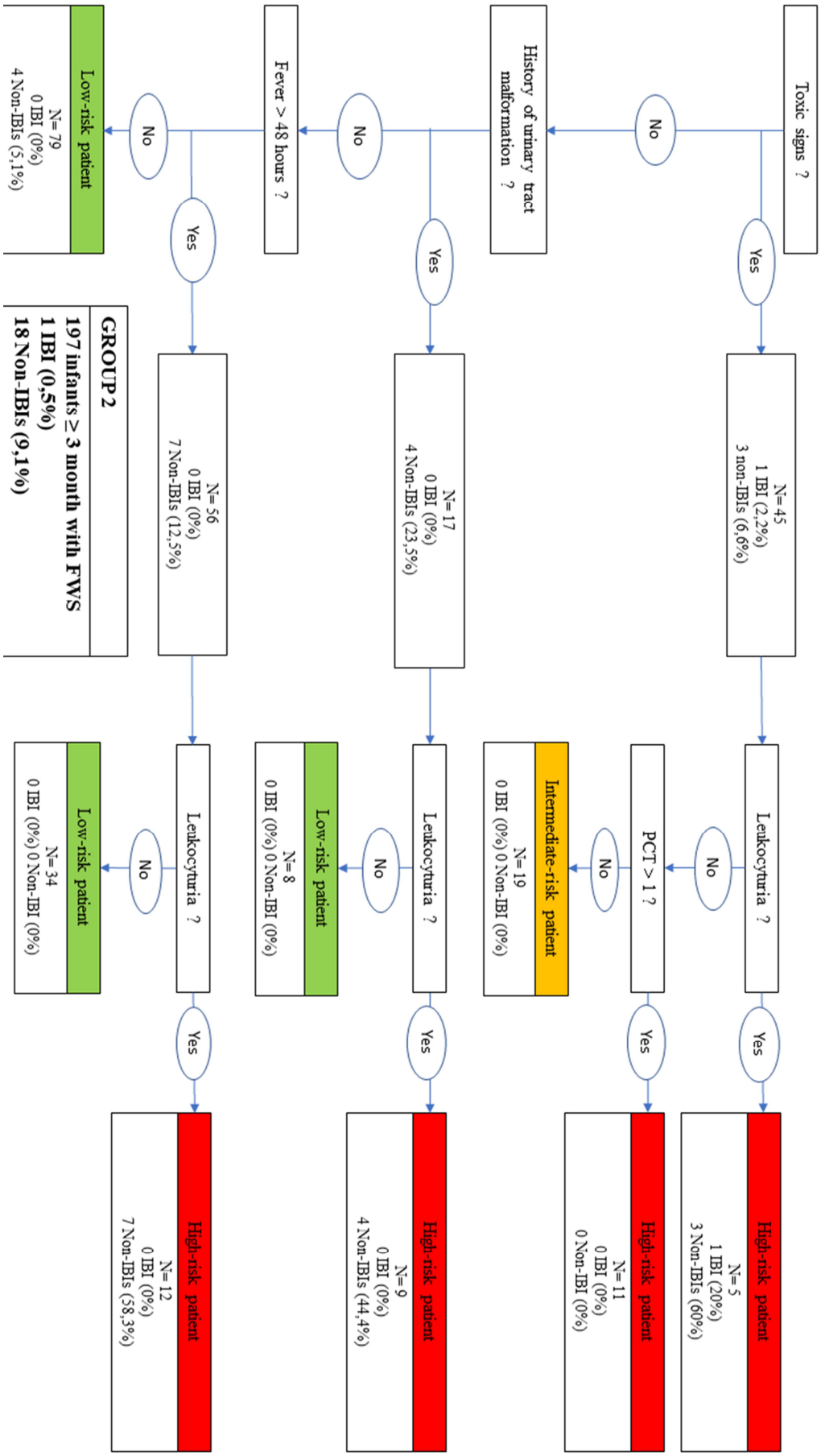


Table S1 Multinomial logistic regression				
	Jacknife analysis SBI		Jacknife analysis IBI	
	RRR (95%CI)	p	RRR (95%CI)	p
Age (months)				
< 1	1		1	
1 to 3	0.88 (0.30-2.61)	0.82	0.39 (0.30-5.13)	0.47
> 3	0.94 (0.29-3.06)	0.92	0.004 (0.0003-0.05)	0.000
Other parameters				
Duration of fever > 48 hrs	1.06 (0.41-2.73)	0.90	36.4 (2.04-649)	0.01
Toxic signs	0.58 (0.26-1.23)	0.17	9.04 (0.96-85.3)	0.05
Leukocyturia	$7.8*10^{8}$ ($3.4*10^{3}$-$1.8*10^{14}$)	0.001	4.44 (0.90-21.9)	0.07
History of urinary tract malformation	1.06 (0.39-2.85)	0.91	$6.9*10^{-8}$ ($2.5*10^{-13}$-0.2)	0.01
PCT > 0,5 ng/ml	2.48 (1.23-5.00)	0.01	19.8 (1.7-229)	0.02

Table S2: characteristics of IBIs

age	duration between onset of fever and samples	gravity signs	toxic signs	comorbidities	leucocyturia (/mm³)	WBC (/mm³)	ANC (/mm³)	CRP (mg/L)	PCT (ng/mL)	urine culture	Hemoculture	Lumbar culture	hospitalisation	Outcome
9d	1 hour	hemodynamic and neurologic	bulging fontanelle, moaning, drowsy	0	2	4090	2440	5,1	7,24	sterile	E. coli K1	sterile	Intensive care unit	no complication
9d	48 hours	0	0	0	10	7000	3560	331,5	5,73	sterile	S. agalactiae	S. agalactiae	Intensive care unit	thrombosis of sagittal sinus, pneumococcal meningitis at 5 months of age
21d	10 hours and 30 min	0	0	0	18 000	13180	8800	11,1	9,5	E. coli >10⁵CFU/mL	E. coli	sterile	classical pediatrical unit	no complication
23d	2 hours and 30 min	0	moaning	0	4	8610	5700	<5	0,24	sterile	S. agalactiae	sterile	classical pediatrical unit	no complication
1 month and 11d	2 hours	0	0	0	2985	18160	9500	142,1	1,08	E. Coli >10⁵CFU/mL	E. coli	-	classical pediatrical unit	no complication
1 month and 11d	7 hours	0	moaning, medical concern	0	14	8060	5570	55,2	1,01	sterile	sterile	sterile	classical pediatrical unit	no complication
1 month and 13d	3 hours	hemodynamic	changed crying patterns, inconsolable, parental and clinical concern	0	18	7550	4880	<5	0,11	sterile	S. agalactiae	sterile	classical pediatrical unit	no complication
4months 26d	48 hours	0	pallor, parental and clinical concern	0	urine dipstick negative	15960	10210	297	30,9	-	N. meningitidis C	N. meningitidis C	Intensive care unit	mild neurological complications (delayed developpement)

8months 2d	72 hours	0	polypnea, parental and clinical concern	0	626	18360	10520	284,3	3,71	E. coli $>10^5$CFU/mL	E. coli	-	no initial hospitalisation	no complication
10m12d	192 hours	neurologic failure	cyanosis, hypotonia	0	urine dipstick negative	38910	22020	159,7	4,82	-	S. pneumoniae st 8	-	no initial hospitalisation	endocarditis, surgical aortic valve replacement, thrombo-embolisis of iliac artery
1 year 2 months 12d	72 hours	hemodynamic, neurologic and respiratory failures	polypnea, hypotonia, parental and medical concern	0	520	3450	2520	187,3	70,24	contaminated	S. pyogenes	-	resucitation unit	death
E=Escherichia, N= Neisseria, S=Streptococcus														

TABLE S3a Diagnostic performances with 95% CI, of the approach for identifying SBIs in group 1

	total	<1 month	1-3 month	>3 months
Sensitivity, %	86.3 [77.7-92.5]	100 [73.5-100]	100 [86.8-100]	77.2 [64.2-87.3]
Specificity, %	82.5 [79.3-85.5]	37.5 [18.8-59.4]	65.1 [55.0-74.2]	98.5 [85.3-91.2]
Positive Likelihood Ratio	5.0 [4.1-6.0]	1.6 [1.2-2.2]	2.8 [2.2-3.7]	6.7 [5.0-8.9]
Negative Likelihood Ratio	0.2 [0.1-0.3]	0 [-]	0 [-]	0.3 [0.2-0.4]
Positive Predictive Value, %	43.4 [38.8-48.1]	44.4 [37.0-52.2]	41.9 [35.7-48.4]	44.0 [37.2-51.1]
Negative Predictive Value, %	97.5 [95.9-98.5]	100 [-]	100 [-]	97.1 [95.3-98.2]

TABLE S3b Diagnostic performances with 95% CI, of the approach for identifying IBIs in group 1

	total	<1 month	1-3 month	>3 months
Sensitivity, %	100 [66.4-100]	100 [29.2-100]	100 [29,2-100]	100 [29.2-100]
Specificity, %	74.2 [70.8-77.4]	27.3 [13.3-45.5]	53.2 [44.1-62.1]	82.0 [78.5-85.2]
Positive Likelihood Ratio	3.9 [3.4-4.4]	1.4 [1.1-1.7]	2.1 [1.8-2.6]	5.6 [4.7-6.7]
Negative Likelihood Ratio	0 [-]	0 [-]	0 [-]	0 [-]
Positive Predictive Value, %	4.8 [4.2-5.4]	11.1 [9.2-13,4]	4.8 [4.1-5.8]	3.0 [2.5-3.6]
Negative Predictive Value, %	100 [-]	100 [-]	100 [-]	100 [-]

TABLE S3c Diagnostic performances with 95% CI, of the approach for identifying SBIs in group 2

	total	<1 month	1-3 month	>3 months
Sensitivity, %	86.2 [68.3-96.1]	100 [29.2-100]	100 [59.0-100]	78.6 [54.4-93.9]
Specificity, %	80.2 [74.2-85.3]	52.9 [27.8-77]	67.6 [50.2-82.0]	86.1 [79.7-91.1]
Positive Likelihood Ratio	4.4 [3.2-5.9]	2.1 [1.3-3.5]	3.1 [1.9-4.9]	5.7 [3.6-8.9]
Negative Likelihood Ratio	0,17 [0.1-0.4]	0 [-]	0 [-]	0.2 [0.1-0.6]
Positive Predictive Value, %	37.3 [30.4-44.7]	27.3 [18.4-38.3]	36.8 [26.8-48.2]	40.5 [30.2-51.7]
Negative Predictive Value, %	97.7 [94.5-99.1]	100 [-]	100 [-]	97.1 [93.4-98,8]

TABLE S3d Diagnostic performances with 95% CI, of the approach for identifying IBIs in group 2

	total	<1 month	1-3 month	>3 months
Sensitivity, %	100 [15.8-100]	100 [2.5-100]	-	100 [2.5-100]
Specificity, %	72.8 [66.7-78.3]	47.3 [24.5-71.1]	56.8 [41-71.7]	79.6 [72.8-85.2]
Positive Likelihood Ratio	3.7 [3.0-4.5]	1.9 [1.2-2.9]	0 [-]	4.9 [3.7-6.5]
Negative Likelihood Ratio	0 [-]	0 [-]	1.8 [-]	0 [-]
Positive Predictive Value, %	3.0 [2.4-3.6]	9.1 [6.1-13,3]	0 [-]	2.7 [2.0-3.6]
Negative Predictive Value, %	100 [-]	100 [-]	100 [-]	100 [-]

III- DISCUSSION ET PERSPECTIVES

Principaux résultats et validité interne

Grace à cet algorithme, basé sur des paramètres cliniques simples, ainsi que sur la bandelette urinaire et la PCT si indiqués, nous pouvions correctement classer 100% des IBIs dans un groupe dit de haut-risque, tout en réduisant potentiellement le taux de prescription d'antibiotique. Seuls 85,6% des IBS étaient identifiées dans les haut-risque. Néanmoins, tous les enfants avec une IBS qui étaient mal classés avaient une infection urinaire débutante, qui fut diagnostiquée lors d'une seconde visite aux urgences pédiatrique. Les cliniciens doivent donc s'assurer que les parents reconsultent en cas de persistance de la fièvre et donner des consignes claires de surveillance au domicile.

Implication pratique et perspectives futures

Le combat contre l'antibiorésistance doit devenir une priorité notamment dans tous les secteurs où la prescription d'antibiotiques est fréquente comme aux urgences pédiatriques. On estime, au niveau mondial, qu'environ 700 000 décès par an seraient attribuables aux résistances aux antibiotiques (17). La relation entre la pression de sélection antibiotique et l'émergence de résistances a été démontrée (15) et la réduction des prescriptions excessives d'antibiotiques peut permettre de réduire la prévalence des résistances aux antibiotiques (15–17).

Une récente revue systématique a étudié les taux de prescription d'antibiotiques aux urgences pédiatriques : les études concernant des populations d'enfants fébriles rapportaient des taux de prescription antibiotique allant entre 15 et 71%. Les prescriptions étaient notamment extrêmement fréquentes chez les patients d'âge

inférieur à 1 an, avec des taux qui variaient selon les études entre 45 et 71%, avec une moyenne pondérée de 58% (44). Lorsque l'on compare ces chiffres à la prévalence des IBS et des IBI dans ces mêmes populations d'enfants fébriles, il semble évident que des efforts doivent être fournis pour améliorer le diagnostic précoce afin de ne réserver l'antibiothérapie qu'aux patients qui en bénéficieront réellement.

C'est dans cette optique que notre présente étude a été réalisée. Celle-ci était une étude préliminaire, ayant permis le lancement d'une plus large étude multicentrique prospective, nommée DIAFEVERCHILD, ayant pour objectif de comparer les prises en charge usuelles des patients fébriles aux urgences pédiatriques de 22 centres en France et en Suisse, à une prise en charge codifiée selon l'algorithme présenté dans ce travail. Cet algorithme est simplement « amélioré » par l'intégration du dosage de la PCT au lit du malade, par une ponction capillaire au bout du doigt (Point-of-care-testing) ce qui permet une diminution de la douleur liée au prélèvement sanguin et des résultats plus rapides. L'objectif principal de cette étude est de démontrer la non-infériorité d'une telle prise en charge en termes de morbi-mortalité. L'objectif secondaire est de démontrer une diminution significative du taux de prescription antibiotique. Cette étude a fait l'objet d'un PHRC et est actuellement en cours de réalisation.

IV- CONCLUSION

Dans cette population de jeunes enfants consultant aux urgences pédiatriques pour une fièvre sans point d'appel, cette nouvelle approche séquentielle identifiant des patients à bas risque d'infection bactérienne a démontré des performances diagnostiques satisfaisantes, avec en particulier une excellente valeur prédictive négative pour exclure les infections bactériennes invasives. Cette approche pourrait permettre une diminution potentielle du taux de prescription antibiotique de 28,3%. La prochaine étape est d'intégrer à cet algorithme le dosage rapide au lit du malade de la PCT et de valider l'intérêt d'une telle approche grâce à une étude multicentrique prospective comparative.

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Vu, le Président du Jury,
(tampon et signature)

Titre Prénom NOM

Vu, le Directeur de Thèse,
(tampon et signature)

Titre Prénom NOM

Vu, le Doyen de la Faculté,

Professeur Pascale JOLLIET

NOM : FEILDEL épouse FOURNIAL PRENOM : Cécile

Titre de Thèse : Valeur diagnostique d'une approche séquentielle pour stratifier le risque d'infection bactérienne invasive aux urgences pédiatriques, et intérêt potentiel d'une telle approche dans la diminution de l'exposition aux antibiotiques

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RESUME (10 lignes)

- **Objectif principal** : Valeur diagnostique d'une approche séquentielle pour identifier les patients à bas risque d'infection bactérienne invasive (IBI) parmi les enfants fébriles consultant aux urgences pédiatriques. **Objectif secondaire** : Intérêt de cette approche dans la diminution de l'exposition aux antibiotiques.

- Matériel et méthodes : Etude prospective observationnelle incluant les enfants ≤ 5 ans se présentant aux urgences pédiatriques du CHU de Nantes pour une fièvre sans point d'appel en 2016. Construction d'un algorithme séquentiel basé sur l'âge, les signes toxiques, les analyses urinaires et la procalcitonine.

- Résultats : Sur les 1061 enfants inclus (IBI 11/1061 1,04%), 693 (65,3%) étaient classifiés en risque bas ou intermédiaire, avec une prévalence d'IBI de 0% [IC 95% 0-0,6]. La sensibilité et la spécificité de cette approche pour prédire les IBI étaient 100% [IC 95% 71,5-100] et 73,9% [IC 95% 70,9-76,7]. L'exposition aux antibiotiques observée était de 33,6%. En utilisant ce nouvel algorithme, nous aurions pu réduire l'exposition à 24,1%, ce qui correspond à une diminution relative de 28,3%.

- Conclusion : Cette nouvelle approche séquentielle a une bonne valeur diagnostique pour identifier les IBI, avec un intérêt potentiel pour diminuer l'exposition aux antibiotiques.

MOTS-CLES

- Fièvre sans point d'appel
- Infection bactérienne invasive
- Procalcitonine
- Epargne antibiotique