Reassessing the Performance of the "Step-By-Step" Approach to Febrile Infants 90 Days of Age and Younger in the Context of the COVID-19 Pandemic

A Multicentric Retrospective Study

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Background: Infants with COVID-19 can often present with fever without source, which is a challenging situation in infants <90 days old. The "step-by-step" algorithm has been proposed to identify children at high risk of bacterial infection. In the context of the COVID-19 pandemic, we aimed to reassess the diagnostic performance of this algorithm.

Methods: We performed a multicentric retrospective study in 3 French pediatric emergency departments between 2018 and 2020. We applied the "step-by-step" algorithm to 4 clinical entities: COVID-19, febrile urinary tract infections (FUTI), invasive bacterial infection (IBI), and enterovirus infections. The main outcome was the proportion of infants classified at high risk (ill-appearing, ≤21 days old, with leukocyturia or procalcitonin level ≥0.5 ng/mL).

Results: Among the 199 infants included, 40 had isolated COVID-19, 25 had IBI, 60 had FUTI, and 74 had enterovirus infection. All but 1 infant with bacterial infection were classified at high risk (96% for IBI and 100% for FUTI) as well as 95% with enterovirus and 82% with COVID-19. Infants with COVID-19 were classified at high risk because an ill-appearance (72%), an age ≤21 days (27%), or leukocyturia (19%). All these infants had procalcitonin values <0.5 ng/mL and only 1 had C-reactive protein level >20 mg/L.

Conclusions: The "step-by-step" algorithm remains effective to identify infants with bacterial infection but misclassifies most infants with COVID-19 as at high risk of bacterial infection leading to unnecessary cares. An updated algorithm based adding viral testing may be needed to discriminate fever related to isolated COVID-19 in infants <90 days old.

Key words: COVID-19, SARS-CoV-2, invasive bacterial infection, urinary tract infection, enterovirus infection, "step-by-step" approach

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Fever without source is a frequent reason for consultation in the pediatric emergency department (PED) in infants <90 days old. This population is at high risk of bacterial infection.[1,2] Although febrile urinary tract infection (FUTI) is the main bacterial infection, physicians worry about invasive bacterial infection (IBI).

Several algorithms have been proposed to identify subgroups of children at high risk of bacterial infection.[2-4] The "step-by-step" approach has been validated with an accuracy superior to the Rochester criteria and Lab-score.[2,5] Children with an ill-appearance, an age ≤21 days, leukocyturia or procalcitonin level ≥0.5 ng/mL are classified as high risk and a full sepsis work-up with parenteral antibiotic treatment during hospitalization is recommended.[2,5]

Self-limiting viral infections are responsible for most febrile episodes[1,2] leading to unnecessary cares and treatments. Among viral infections, enterovirus infections have variable clinical presentations, from well-tolerated isolated fever to sepsis-like syndrome.[6,7] Since 2020, COVID-19 is a new cause of fever in young infants and may be frequent in this age group, especially during the epidemic waves.[8] Sepsis-like appearance has been described in some infants with COVID-19, which raises concerns about the possibility to differentiate them from bacterial infection.[8,9]

In this context, we aimed to reassess the "step-by-step" algorithm performance and describe the clinical presentations and management in children <90 days old who have fever without a source related to COVID-19 in comparison to IBI, FUTI, and enterovirus infections.

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The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee (Robert Debré Pediatric Hospital) and informed consent from parents was not required.

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MATERIALS AND METHODS

We conducted a multicentric retrospective study in 3 PEDs located in the Paris area, France.

Population

We included consecutively all febrile infants <90 days old with a diagnosis of COVID-19, enterovirus infection, or IBI who visited a participating PED between January 2018 and December 2020. Infants with a diagnosis of FUTI during the same period were randomly selected in each center to have at least as many patients as in the COVID-19 group.

COVID-19 was defined as a positive SARS-CoV-2 nasopharyngeal PCR test with no evidence of bacterial infection (absence of positive blood culture, urine culture, and cerebrospinal fluid culture). We only used laboratory PCR tests. Enterovirus infection was defined as a positive enterovirus PCR test on cerebrospinal fluid or blood. FUTI was defined as fever, pyuria (positive urinary dipstick test or leukocyte count ≥10,000/mL) and a positive culture with ≥50,000 colony-forming units/mL of a single uropathogen. IBI was defined as bacteremia (with or without FUTI) or bacterial meningitis (with or without bacteremia). Blood and urines cultures were counted as negative when the clinician considered them to be contaminated.

Children were identified from diagnosis coded in their electronic medical record and from microbiologic laboratories. Children with a diagnosis of viral infection were screened for a second visit, using their electronic medical record, during the week after being discharged.

Outcomes

The main outcome was the proportion of infants with isolated COVID-19 who were classified at high risk of bacterial infection based on the "step-by-step" algorithm.[2,5] This group corresponds to infants with an ill-appearance according to the Pediatric Assessment Triangle,[10] ≤21 days old, with leukocyturia and procalcitonin level ≥0.5 ng/mL. The remaining infants with C-reactive protein (CRP) level >20 mg/L or absolute neutrophil count (ANC) >10,000/mm^3 were classified in the intermediate-risk group and with none of these criteria in the low-risk group.

Secondary objectives were to compare the clinical characteristics, treatments, clinical outcomes, and biologic characteristics of infants with COVID-19 and with an enterovirus infection, IBI or FUTI.

Statistics

Categorical data are described with absolute and relative frequencies and quantitative data with median and interquartile range. We compared two-by-two categorical and quantitative variables between the COVID-19 group and the other groups by Fisher exact test and Mann-Whitney *U* test, applying Bonferroni correction to adjust for the multiple comparisons, with $P < 0.015$ considered statistically significant.[11] Missing values were considered to be normal. All analyses were performed with Stata 15.1 (StataCorp LLC, College Station, TX, USA).

Ethics

Approval was granted by the local Ethics Committee (Robert Debré Pediatric Hospital). Informed consent from parents was not required.

RESULTS

During the study period, we included 199 children: 40 with COVID-19, 74 with enterovirus infection, 25 with IBI, and 60 with FUTI. When presenting at the PED, the temperature was normal for 51 (26%) infants. Among children in the IBI group, 14 had FUTI with bacteremia, 9 isolated bacteremia and 4 bacterial meningitis.

Among the 40 children with isolated COVID-19, the most common symptom was fever (39/40, 87%), followed by feeding difficulties (19/40, 47%), and discomfort (12/40, 30%). Overall, 17/40 (42%) infants had rhinitis, with abnormal capillary refill time, mottling and hypotonia described in 7/40 (17%), 5/40 (12%), and 5/40 (12%), respectively. As compared with infants with COVID-19, those with IBI and FUTI less frequently had close contact with someone who was sick (26/40, 67% vs. 4/25, 16% and 14/60, 23%, respectively, all $P < 0.001$). The proportion of ill-appearing children was comparable between the COVID-19 group and other groups (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/E759).

Infants with isolated COVID-19 were frequently hospitalized (31/40, 77%) and their median hospital stay was 1 day (and interquartile range 1–3). Only 9 of 40 (22%) received antibiotics and 3 of 40 (7%) required a fluid bolus. They had all favorable clinical outcomes, with no admission to an intensive care unit (management and clinical outcomes are detailed in Table, Supplemental Digital Content 2, http://links.lww.com/INF/E759).

Among the 85 children with bacterial infections, 84 (99%) were classified at high risk according to the step-by-step approach (Table 1). One child, a 40-day-old girl, late preterm, had a occult *Streptococcus agalactiae* bacteremia and was classified in the low-risk group. She presented to the PED with fever and a rhinitis. Both CRP and procalcitonin were at normal levels at <6 hours after the beginning of the fever.

Urinalysis was performed for 191 children (96%), blood culture for 172 children (86%), and lumbar puncture for 120 children (60%). Among the 114 children with isolated viral infections, 102 (90%) were in the high-risk group. Furthermore, 32 of 40 (82%) children with isolated COVID-19 were classified in the high-risk group mostly because of an ill-appearance (29/40, 72%), an age ≤21 days (11/40, 27%) or leukocyturia (7/36, 19%). For all infants with COVID-19, when tested, procalcitonin level was <0.5 ng/mL and ANC <10,000/mm^3. For all but 1 infant, the CRP level was ≤20 mg/L (24 mg/L for 1 infant). Children visiting during the COVID-19 pandemic had less lumbar puncture performed (41% vs. 69%, $P < 0.0001$) but similar blood culture (80% vs. 89%, $P = 0.1$) and urinary analysis (93% vs. 98%, $P = 0.06$). Biologic characteristics are detailed in Table, Supplemental Digital Content 3, http://links.lww.com/INF/E759.

One infant had a positive SARS-CoV-2 test (unknown cycle threshold) and a FUTI. Finally, no bacterial infection was identified among children with enterovirus infection. To our knowledge, no bacterial infections have been diagnosed during a second PED visit in children being discharged after their first PED visit.

DISCUSSION

Here, we classified the risk of bacterial infection infants by the "step-by-step" approach in infants <90 days old who presented to PED. Furthermore, we describe the clinical and biologic characteristics, and management of febrile infants with COVID-19 and compare them to febrile children with IBI, FUTI, and enterovirus infections. Despite the rarity of complication and associated bacterial infections, most infants with COVID-19 and enterovirus infections had an ill-appearance when presenting to the PED, so they were often classified in the high-risk group by the "step-by-step" approach. The strict application of this algorithm would have led to frequent and unnecessary antibiotics prescriptions for infants with COVID-19. This finding is in accordance with the objective of algorithms to prioritize sensibility over specificity. Of note, the proportion of antibiotics prescriptions in children with COVID-19

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TABLE 1. "Step-by-step" Approach Criteria and Risk Levels for Bacterial Infections for Infants Included in the Study

Group	Isolated Viral Infection N = 114	Isolated COVID-19 N = 40	Enterovirus Infection N = 74	All Bacterial Infections N = 85	IBI N = 25	FUTI N = 60	All Infants N = 199
Ill-appearance	89/114 (78%)	29/40 (72%)	60/74 (81%)	59/85 (69%)	21/25 (84%)	38/60 (63%)	148/199 (74%)
Age ≤21 d	43/114 (38%)	11/40 (27%)	32/74 (43%)	24/85 (28%)	14/25 (56%)	10/60 (17%)	67/199 (34%)
Leukocyturia	28/106 (26%)	7/36 (19%)	21/70 (30%)	79/85 (93%)	19/25 (76%)	60/60 (100%)	107/191 (56%)
Procalcitonin level ≥0.5 ng/mL	10/91 (11%)	0/28 (0%)	10/63 (16%)	38/64 (59%)	17/21 (81%)	21/43 (49%)	48/155 (31%)
CRP level >20 mg/L	19/103 (18%)	1/33 (3%)	18/70 (26%)	56/79 (71%)	15/24 (62%)	41/55 (74%)	95/182 (52%)
ANC >10,000/mm^3	1/101 (1%)	0/29 (0%)	1/72 (1%)	21/74 (28%)	7/23 (30%)	14/51 (27%)	22/175 (13%)
Risk according to the step-by-step algorithm							
Low	8 (7%)	5 (13%)	3 (4%)	1 (1%)	1 (4%)	0	9 (4%)
Intermediate	3 (3%)	2 (5%)	1 (1%)	0	0	0	3 (2%)
High	102 (90%)	32 (82%)	70 (95%)	84 (99%)	24 (96%)	60 (100%)	186 (94%)

ANC indicates absolute neutrophil count; CRP, C-reactive protein; FUTI, febrile urinary tract infection; IBI, invasive bacterial infection.

was surprisingly low. This attitude suggests that clinicians often do not consider children with a positive SARS-CoV-2 test as belonging to the high-risk group despite an ill-appearance. Furthermore, we observed that children during the COVID-19 had less lumbar puncture performed. Although the National guidelines have not been changed during the study period, this could be an illustration of the trend to limit the use of this examination.

Interestingly, children with isolated enterovirus infection had a higher antibiotic prescription rate than children with isolated COVID-19 (84% vs. 22%, $P < 0.001$). This could be explained by differences in the clinical and biologic characteristics with younger children, higher rate of ill-appearing children, and higher CRP levels in children with enterovirus infection. Furthermore, enterovirus PCR in often performed on cerebrospinal fluid selecting children for which a lumbar puncture was performed. Recently, the American Association of Pediatrics published guidelines on management in well-appearing febrile infants ≤60 days old.[3] Infants >21 days with a positive test for enterovirus, no leukocyturia and normal inflammatory marker levels can be cared for at home. These criteria were met for 12/74 (16%) infants in our study. Apart from this particular situation, a positive viral test does not influence management despite bacterial infections being less frequent in this subgroup.[3] This situation highlights the need for new algorithms including in addition viral testing.

All infants with bacterial infection except for 1 child with *Streptococcus agalactiae* occult bacteremia were classified in the high-risk group. This child may have been misclassified because of early inflammatory markers dosage as for 73 of 176 (41%) infants in our study who had a blood test performed <6 hours after the beginning of the fever. Although frequent and at risk of misclassification, this situation is not individualized in algorithms.[2,3,5] Clinicians should be aware of this risk and may perform a second testing of inflammatory markers or a hospital surveillance. Furthermore, 1 child in 41 with a positive SARS-CoV-2 test and none of the 74 with a positive enterovirus PCR test had a diagnosis of bacterial coinfection, and this FUTI has been detected by the "step-by-step" approach.

Some limitations should be discussed. The use of SARS-CoV-2 test was highly variable during the study period and across the participating centers (from febrile respiratory distress requiring a hospitalization to almost systematic) and only PCR were used. The temporal link between SARS-CoV-2 test result and the use of other tests (blood culture, urinalysis, and lumbar puncture) was not evaluated. We cannot exclude that some parents feared consulting at the beginning of the epidemic. Furthermore, only the original SARS-CoV-2 strain was circulating during the study period. The omicron variant has led to milder disease in adults,[12] and a similar trend is possible in infants. Moreover, we cannot exclude that patients were diagnosed with a bacterial infection after visiting a different hospital. Finally, because of the retrospective design and missing data, we cannot exclude that the 12 children in the low and intermediate-risk group may have been misclassified. However, missing value in this subgroup concern only few children (missing PCT and ANC levels for 2 children, missing leukocyturia and CRP value for 1 child), whereas age and clinical appearance was available for all children. By contrast, missing values could not have changed the classification of children in the high-risk group because the presence of at least 1 criteria is required to be classified in this group regardless of other criteria.

Overall, as for enterovirus infection, infants with COVID-19 can present a sepsis-like syndrome, which challenges the "step-by-step" algorithm to discriminate this infection from IBI. However, inflammatory values are rarely elevated in children with COVID-19, which may help clinicians in the care of these children and call for an updated algorithm including in addition viral testing. Further studies are required to evaluate prospectively the performance of this algorithm in children with COVID-19 and to develop an updated algorithm which will include viral testing.

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REFERENCES

1. Milcent K, Faesch S, Gras-Le Guen C, et al. Use of procalcitonin assays to predict serious bacterial infection in young febrile infants. *JAMA Pediatr.* 2016;170:62–69.
2. Mintegi S, Bressan S, Gomez B, et al. Accuracy of a sequential approach to identify young febrile infants at low risk for invasive bacterial infection. *Emerg Med J.* 2014;31(e1):e19–e24.
3. Pantell RH, Roberts KB, Adams WG, et al; Subcommittee on Febrile Infants. Evaluation and management of well-appearing febrile infants 8 to 60 days old. *Pediatrics.* 2021;148:e2021052228.
4. Hubert G, Launay E, Feildel Fournial C, et al. Assessment of the impact of a new sequential approach to antimicrobial use in young febrile children in the emergency department (DIAFEVERCHILD): a French prospective multicentric controlled, open, cluster-randomised, parallel-group study protocol. *BMJ Open.* 2020;10:e034828.
5. Gomez B, Mintegi S, Bressan S, et al; European Group for Validation of the Step-by-Step Approach. Validation of the "Step-by-Step" approach in the management of young febrile infants. *Pediatrics.* 2016;138:e20154381.
6. de Crom SC, van Furth MA, Peeters MF, et al. Characteristics of pediatric patients with enterovirus meningitis and no cerebral fluid pleocytosis. *Eur J Pediatr.* 2012;171:795–800.
7. de Crom SC, Rossen JW, van Furth AM, et al. Enterovirus and parechovirus infection in children: a brief overview. *Eur J Pediatr.* 2016;175:1023–1029.
8. Mark EG, Golden WC, Gilmore MM, et al. Community-onset severe acute respiratory syndrome coronavirus 2 infection in young infants: a systematic review. *J Pediatr.* 2021;228:94–100.e3.

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9. Bellini T, Rotulo GA, Caruggi S, et al. Characteristics of COVID-19 patients up to 6 months of age admitted to a paediatric emergency department. *Acta Paediatr.* 2022;111:272–274.

10. Dieckmann RA, Brownstein D, Gausche-Hill M. The pediatric assessment triangle: a novel approach for the rapid evaluation of children. *Pediatr Emerg Care.* 2010;26:312–315.

11. Gelman A, Hill J, Yajima M. Why we (Usually) don't have to worry about multiple comparisons. *J Res Educ Eff.* 2012;5:189–211.

12. Veneti L, Boas H, Brathen Kristoffersen A, et al. Reduced risk of hospitalisation among reported COVID-19 cases infected with the SARS-CoV-2 Omicron BA.1 variant compared with the Delta variant, Norway, December 2021 to January 2022. *Euro Surveill*. 2022;27.

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