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

Alexis Rybak, MD,†† Camille Aupiais, PhD,‡§ Marie Cotillon, MD,¶ Romain Basmaci, PhD,¶¶ Loïc de Pontual, PhD,§ Stéphane Bonacorsi, PhD,¶¶¶ Patricia Mariani, MD,¶¶ Lucre Landraud, PhD,†† Ségolène Brichler, PhD,‡‡ Isabelle Poilane, PharmaD,‡‡ Naïm Ouladali, PhD,¶¶¶¶ Luigi Titomanlio, PhD*¶¶

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 of 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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From the *Pediatric Emergency Department, Robert Debré University Hospital, Université de Paris, Assistance Publique—Hôpitaux de Paris, Paris, France; †Association Clinique et Thérapeutique Infantile du Val-de-Marne (ACTIV), Créteil, France; ‡INSERM, Unité Mixte de Recherche 1123 Épidémiologie Clinique et Évaluation Économique Appliquées aux Populations Vulnérables (ECEVE), Université de Paris, Paris, France; §Department of Pediatrics, Jean Verdier University Hospital, Assistance Publique—Hôpitaux de Paris, Université Sorbonne Paris Nord, Bondy, France; ¶Department of Pediatrics, Louis Mourier University Hospital, Université de Paris, Assistance Publique—Hôpitaux de Paris, Colombes, France; ¶¶Infectious Diseases Division, CHU Sainte Justine—Montreal University, Montreal, Quebec, Canada; and ¶¶¶Inserm, Unité Mixte de Recherche 1141 Infection-Antimicrobials-Modelling-Evolution (IAME), Université de Paris, Paris, France; ||Department of Microbiology, Robert Debré University Hospital, Université de Paris, Assistance Publique—Hôpitaux de Paris, Paris, France; ††Department of Microbiology, Louis Mourier University Hospital, Université de Paris, Assistance Publique—Hôpitaux de Paris, Colombes, France; ‡‡Department of Clinical Microbiology, Paris-Seine-Saint-Denis University Hospitals, Université Sorbonne Paris Nord, Assistance Publique—Hôpitaux de Paris, Bobigny, France; §§Department of General Pediatrics, Pediatric Infectious Disease and Internal Medicine, Robert Debré University Hospital, Université de Paris, Assistance Publique—Hôpitaux de Paris, Paris, France; ¶¶¶¶Infectious Diseases Division, CHU Sainte Justine—Montreal University, Montreal, Quebec, Canada; and IINSERM, Unité Mixte de Recherche 1141 DHU Protect, Université de Paris, Paris, France.

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Address for correspondence: Alexis Rybak, MD, Pediatric Emergency Department—Robert Debré University Hospital, Assistance Publique—Hôpitaux de Paris, 48, Boulevard Sévérail 75019 Paris, France. E-mail: alexis.rybak@aphp.fr.

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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 $\geq 10,000$/mL) and a positive culture with $\geq 50,000$ 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. This group corresponds to infants with an ill-appearence according to the Pediatric Assessment Triangle, with $\geq 21$ days old, with leukocyturia and procalcitonin level $\geq 0.5$mg/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. 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 rhenitis, with abnormal capillary refill time, motility 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 rhenitis. 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-appearence (29/40, 72%), an age $\leq 21$ days (11/40, 27%) or leukocyturia (7/36, 19%). All infants with COVID-19, when tested, procalcitonin level was <0.5mg/mL and ANC $<10,000$/mm$^3$. For all but 1 infant, the CRP level was $\leq 20$mg/L (24mg/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-appearence 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...
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 for well-appearing febrile infants ≤60 days old. 3 Infants >21 days can present a sepsis-like syndrome, which challenges the “step-by-step” algorithm in children with COVID-19. 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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