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Reassessing the performance of the “step-by-step” approach to febrile infants aged 90 days and younger in the context of the COVID-19 pandemic: a multicentric retrospective study

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Research Article

Keywords: COVID-19, SARS-CoV-2, invasive bacterial infection, urinary tract infection, enterovirus infection, “step-by-step” approach.

Posted Date: March 24th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1441264/v1

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Abstract

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 four 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.

Results

Among the 199 infants included, 40 had isolated COVID-19, 25 had IBI, 60 had FUTI, and 74 had enterovirus infection. All but one 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%) and/or leukocyturia (19%). All these infants had procalcitonin values < 0.5 ng/mL and only one 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.

Background

Fever without source is a frequent reason for consultation in the pediatric emergency department (PED) in infants aged 90 days and younger. 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

and/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.

Methods

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

Population

We included all infants aged 90 days and less 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 included 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. 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.

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], aged 21 days and younger, with leukocyturia and/or procalcitonin level ≥ 0.5 ng/mL. The remaining infants with CRP level > 20 mg/L or 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 biological 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 (IQR). 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]. All analyses were performed with Stata 15.1 (StataCorp LLC, College Station, TX, USA). A standardized anonymous electronic case report form was used to obtain medical information in each participating center.

Ethics

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.

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 (Table 1).

Table 1
Clinical characteristics of infants aged 90 days and younger included in the study

	Isolated COVID-19 **N = 40**	**Isolated enterovirus infection** **N = 74**	**IBI** **N = 25**	**FUTI** **N = 60**	**All infants** **N = 199**
Male, n (%)	24 (60%)	43 (58%)	13 (52%)	44 (73%)	124 (62%)
Age (days), median (IQR)	34 (19–53)	23 (12–36)**	21 (14–34)	58 (41–76)**	33 (17–53)
Preterm, n (%)	1 (3%)	3 (4%)	6 (24%)*	6 (11%)	16 (8%)
Complex chronic condition, n (%)	1 (2%)	1 (1%)	1 (4%)	4 (7%)	7 (3%)
History of urinary tract infection, n (%)	1 (2%)	0	1 (4%)	2 (3%)	4 (2%)
Close contact with someone with someone who was sick, n (%)	26 (67%)	42 (57%)	4 (16%)***	14 (23%)***	86 (43%)
Main purpose for consultation, n (%) Fever Shortness of breath	35 (87%) 4 (10%)	73 (99%) 0	21 (84%) 1 (4%)	58 (98%) 0	187 (94%) 5 (3%)
Duration of symptoms (days), median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)

Abbreviations: IQR, interquartile range; FUTI, febrile urinary tract infection; IBI, invasive bacterial infection

Compared to the COVID-19 group: * $p < 0.015$, ** $p < 0.01$, *** $p < 0.001$

	Isolated COVID-19 N = 40	Isolated enterovirus infection N = 74	IBI N = 25	FUTI N = 60	All infants N = 199
Symptoms at home, n (%)	39 (97%)	73 (99%)	24 (96%)	59 (98%)	195 (98%)
Fever	8 (20%)	4 (5%)	3 (12%)	7 (12%)	22 (11%)
Cough	6 (15%)	2 (3%)	1 (4%)	0**	9 (5%)
Dyspnea	2 (5%)	3 (4%)	3 (12%)	13 (22%)	21 (11%)
Vomiting	5 (12%)	12 (16%)	2 (8%)	8 (13%)	27 (14%)
Diarrhea	12 (30%)	41 (55%)*	14 (56%)	17 (28%)	84 (42%)
Discomfort	19 (47%)	24 (32%)	8 (32%)	16 (27%)	67 (34%)
Feeding difficulties					
Temperature at presentation in PED for patients with fever, median (IQR)	38.1 (37.7–38.4)	38.5 (38.1–38.8)**	38.5 (37.9–38.9)	38.2 (37.7–38.6)	38.3 (37.9–38.7)
Maximal temperature at home for patients with fever, median (IQR)	38.5 (38.2–38.7)	38.7 (38.5–39)	38.7 (38.3–38.8)	38.9 (38.5–39)**	38.6 (38.4–39)
Ill-appearing, n (%)	29 (72%)	60 (81%)	21 (84%)	38 (63%)	148 (74%)

Abbreviations: IQR, interquartile range; FUTI, febrile urinary tract infection; IBI, invasive bacterial infection

Compared to the COVID-19 group: * $p < 0.015$, ** $p < 0.01$, *** $p < 0.001$

	Isolated COVID-19 N = 40	Isolated enterovirus infection N = 74	IBI N = 25	FUTI N = 60	All infants N = 199
Physical examination, n (%)	7 (17%)	4 (5%)	2 (8%)	4 (7%)	17 (8.5%)
Abnormal capillary refill time	5 (12%)	19 (26%)	6 (24%)	13 (22%)	43 (22%)
Mottling	0	0	0	0	0
Hepatomegaly	0	7 (10%)	2 (8%)	2 (3%)	12 (6%)
Cold extremities	2 (5%)	3 (4%)	0	2 (3%)	7 (4%)
Cardiac murmur	0	8 (11%)	3 (12%)	1 (2%)	12 (6%)
Chest retractions	0	0	0	0	0
Wheezing	5 (12%)	1 (1%)	1 (4%)	0**	11 (5.5%)
Hypotonia	0	1 (1%)	1 (4%)	0	2 (1%)
Bulging anterior fontanelle	4 (10%)	24 (32%)*	9 (36%)	3 (5%)	40 (20%)
Irritability	1 (2%)	4 (5%)	0	1 (2%)	6 (3%)
Rash	17 (42%)	14 (19%)**	1 (4%)**	11 (18%)*	43 (22%)
Rhinitis	0	0	0	0	0
Acute otitis media					

Abbreviations: IQR, interquartile range; FUTI, febrile urinary tract infection; IBI, invasive bacterial infection

Compared to the COVID-19 group: * $p < 0.015$, ** $p < 0.01$, *** $p < 0.001$

Infants with isolated COVID-19 were frequently hospitalized (31/40, 77%) and their median hospital stay was 1 day (IQR 1–3). Only 9/40 (22%) received antibiotics and 3/40 (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 2).

Table 2
Treatments and clinical outcomes of infants included in the study

Group	Isolated COVID-19 N = 40	Isolated enterovirus infection N = 74	IBI N = 25	FUTI N = 60	All infants N = 199
Fluid bolus, n (%)	3 (7%)	5 (7%)	4 (16%)	2 (3%)	14 (7%)
Analgesic requirement (other than acetaminophen), n (%)	0	1 (1%)	1 (4%)	0	2 (1%)
Oxygen supplementation, n (%)	3 (7%)	2 (3%)	2 (8%)	0	7 (3.5%)
Antibiotic treatment, n (%)	9 (22%)	59 (84%)***	24 (96%)***	60 (100%)***	155 (78%)
Antibiotic initiation at the PED	9 (100%)	56 (95%)	24 (100%)	60 (100%)	152 (98%)
Antibiotic initiation during hospitalization	0	3 (5%)	0	0	3 (2%)
Hospitalization after PED visit, n (%)	31 (77%)	74 (100%)***	23 (92%)	49 (82%)	177 (89%)
Need for pediatric intensive care unit, n (%)	0	1 (1%)	1 (4%)	0	2 (1%)
Death, n (%)	0	0	1 (4%)	0	1 (< 1%)
Length of hospital stay, days, median (IQR)	1 (1–3)	2 (2–3)	7 (5–10)***	2 (1–4)*	3 (1–4)

Abbreviations: PED, pediatric emergency department; IQR, interquartile range; FUTI, febrile urinary tract infection; IBI, invasive bacterial infection

Compared to the COVID-19 group: * $p < 0.015$, ** $p < 0.01$, *** $p < 0.001$

Among the 85 children with bacterial infections, 84 (99%) were classified at high risk according to the step-by-step approach (Table 3). One child, a 40-day-old girl, born at 35 weeks of gestation, 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 hr after the beginning of the fever.

Table 3
"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 days	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%)

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

Among the 114 children with isolated viral infections, 102 (90%) were in the high-risk group. Furthermore, 32/40 (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 one infant, the CRP level was ≤ 20 mg/L (for one infant, the CRP level was 24 mg/L). Biological characteristics are detailed in Table 4.

Table 4
Biological characteristics of infants included in the study

Group	Isolated COVID-19 N = 40	Enterovirus infection N = 74	IBI N = 25	FUTI N = 60	All infants N = 199
Time between fever and blood test, n (%)	4 (10%)	4 (5%)	6 (24%)	9 (15%)	23 (11%)
Missing data or no blood test	17 (47%)	33 (47%)	12 (63%)	11 (21%)	73 (41%)
< 6 hours	5 (14%)	20 (29%)	3 (17%)	12 (24%)	40 (23%)
6–12 hours	4 (11%)	10 (14%)	2 (10%)	10 (20%)	26 (15%)
12–24 hours	10 (28%)	7 (10%)	2 (10%)	18 (35%)	37 (21%)
> 24 hours					
ANC performed, n (%)	29 (72%)	72 (98%)	23 (92%)	51 (85%)	175 (88%)
ANC, median (IQR)	2500 (1600–3700)	4500 (3000–6900)***	7600 (5200-12,800)***	7400 (4900-10,300)***	5100 (3000–7900)
CRP test performed, n (%)	33 (82%)	70 (95%)	24 (96%)	55 (92%)	182 (91%)
CRP level, median (IQR)	2 (0–4)	7 (0–21)**	69 (8-126)***	32 (19–72)***	12 (2–39)
Procalcitonin test performed, n (%)	28 (70%)	63 (85%)	21 (84%)	43 (72%)	155 (78%)
Procalcitonin level, median (IQR)	0.1 (0-0.2)	0.2 (0.1–0.3)*	3.6 (1–21)***	0.4 (0.1–3.1)**	0.2 (0.1-1)
Urinalysis performed, n (%)	36 (90%)	70 (95%)	25 (100%)	60 (100%)	191 (96%)
Blood culture, n (%)	30 (75%)	72 (97%)***	25 (100%)*	45 (75%)	172 (86%)
Lumbar puncture performed, n (%)	14 (35%)	71 (96%)***	20 (80%)**	15 (25%)	120 (60%)
Viral testing, n (%)	40 (100%)	32 (43%)***	6 (24%)***	9 (15%)***	87 (44%)
Positive SARS-CoV-2 test, n (%)	40 (100%)	0***	0***	1 (2%)***	41 (21%)

Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; IQR, interquartile range; UTI, urinary tract infection; IBI, invasive bacterial infection

Compared to the COVID-19 group: * $p < 0.015$, ** $p < 0.01$, *** $p < 0.001$

Group	Isolated COVID-19 N = 40	Enterovirus infection N = 74	IBI N = 25	FUTI N = 60	All infants N = 199
Chest X-ray, n (%)	14 (35%)	31 (42%)	13 (52%)	6 (10%)**	64 (32%)
Pulmonary condensation, n (%)	0	1	1	0	2
Abbreviations: ANC, absolute neutrophil count; CRP, C-reactive protein; IQR, interquartile range; UTI, urinary tract infection; IBI, invasive bacterial infection					
Compared to the COVID-19 group: * $p < 0.015$, ** $p < 0.01$, *** $p < 0.001$					

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 aged 90 days and younger who presented to PED. Furthermore, we describe the clinical and biological characteristics, and management of COVID-19 in febrile and compare them to 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 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.

Recently, the American Association of Pediatrics published guidelines on management in well-appearing febrile infants aged 60 days and younger [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 doesn’t influence management [3] despite bacterial infections being less frequent in this subgroup [12, 13]. This situation highlights the need for new algorithms including in addition viral testing.

All infants with bacterial infection except for one 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 73/176 (41%) infants in our study who had a blood test performed < 6 hr 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, one 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 co-infection, 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. We cannot exclude that some parents presented a fear of consulting in the PED at the beginning of the epidemic [14]. Furthermore, only the original SARS-CoV-2 strain was circulating during the study period. The omicron variant has led to milder disease in adults [15], and a similar trend is possible in infants.

Conclusions

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.

Abbreviations

ANC, absolute neutrophil count

CRP, C-reactive protein

FUTI, febrile urinary tract infection

IBI, invasive bacterial infection

IQR, interquartile range

PED, pediatric emergency department

Declarations

Ethics Approval and consent to participate

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.

Consent for publication

Non applicable

Availability of data and material

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

Competing interests

The authors have no financial or non-financial interest that are directly or indirectly related to the work submitted for publication to disclosure.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Code availability

Not available

Authors' contributions

All authors contributed to the study conception and design. Methodology: AR, CA, NO, and LT. Formal analysis and investigation: AR, CA, MC, RB, LP, SBo, PM, LL, SBr, IP, NO, and LT. Writing - original draft preparation: AR. Writing - review and editing: AR, CA, MC, RB, LP, SBo, PM, LL, SB, IP, NO, and LT; Supervision: AR, CA, NO and LT. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We thank Laura Smales (https://www.biomediediting.com/) for he help with English language editing.

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