

Evaluating Uncommon Inflammatory Markers in Common Pediatric Bacterial Infections

Christina M. McKinney, MD; Michelle L. Mitchell, MD; Erin Preloger, MD; Kelly Graff, MD; Amy Y. Pan, PhD; Melodee Liegl, MA; Glenn Bushee, MS; Patrick J. McCarthy, MD, MME; Vanessa McFadden, MD, PhD; Sarah Corey Bauer, MD

ABSTRACT

Background: Expected ranges for several inflammatory markers in children were poorly defined during the COVID-19 pandemic, making it difficult to distinguish common infections from multisystem inflammatory syndrome in children (MIS-C). We evaluated less commonly obtained inflammatory markers in children with common bacterial infections.

Methods: We completed a retrospective cohort study at a tertiary children's hospital from March 2018 through April 2023 of hospitalized patients >60 days to 21 years with cellulitis, community-acquired pneumonia, or urinary tract infection.

Results: A total of 973 patients were included (median age, 5.6 years; interquartile range, 1.9-12.2; 61% female). Most inflammatory markers were elevated across infections, whereas troponin levels remained within the reference range for all diagnoses.

Discussion: We report values for less commonly obtained inflammatory markers in children hospitalized with common bacterial infections. Normal troponin levels may help distinguish these infections from MIS-C, which more commonly involves cardiac inflammation. Further research is needed to define clinically useful cutoff values for inflammatory markers to aid decision-making in the setting of emerging disease processes.

• • •

Author affiliations: Division of Hospital Medicine, Cincinnati Children's Hospital Medical Center, and Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio (McKinney); Division of Infectious Diseases, Department of Pediatrics, Medical College of Wisconsin (MCW), Milwaukee, Wisconsin (Graff, Mitchell); Section of Pediatric Hospital Medicine, Department of Pediatrics, MCW, Milwaukee, Wisconsin (Corey Bauer, McFadden, Preloger); Division of Bioinformatics and Quantitative Child Health, Department of Pediatrics, MCW, Milwaukee, Wisconsin (Pan, Liegl); Department of Quality and Safety, MCW, Milwaukee, Wisconsin (Bushee); Aurora Children's Health, Advocate Aurora Health, Milwaukee, Wisconsin (McCarthy).

Corresponding author: Christina M. McKinney, MD, 3333 Burnet Ave, MLC 9016, Cincinnati, OH, 45229; email christina.mckinney@cchmc.org; ORCID ID 0009-0002-9372-7980

INTRODUCTION

When evaluating febrile children during the COVID-19 pandemic, multisystem inflammatory syndrome in children (MIS-C) was often included in the differential diagnosis, for which no pathognomonic features are known.^{1,2} Many children, especially those requiring hospitalization, received a broad workup for MIS-C yet were ultimately diagnosed with a common illness that did not require extensive testing. Prior to the emergence of MIS-C, it was uncommon to routinely obtain inflammatory markers (IM) in the evaluation of febrile children. For example, in patients with urinary tract infections (UTIs), a urinalysis and urine culture are often sufficient for diagnosis. The diagnosis of community-acquired pneumonia (CAP) can often be made clinically or with a chest x-ray. In patients with cellulitis,

laboratory testing is often not required.

Occasionally, laboratory tests including C-reactive protein (CRP), procalcitonin, a complete blood count (CBC), or erythrocyte sedimentation rate (ESR) can be helpful in stratifying disease severity or response to treatment; however, children admitted to a general hospital medicine service with these conditions typically do not require extensive laboratory testing. During the pandemic, however, given the overlapping features of these infections with MIS-C, many of these patients underwent a more extensive laboratory workup, which included less commonly obtained tests such as ferritin, D-dimer, troponin, and N-terminal pro-B-type natriuretic peptide (BNP), as specified in the MIS-C diagnostic algorithm. These laboratory values were often non-specifically elevated in both patients with MIS-C and those with

Table. Inflammatory Markers by Diagnosis								
	n eval	Cellulitis (n=403)	n eval	Pneumonia (n=158)	n eval	UTI (n=412)	n eval	MIS-C Data ² (n=16)
C-reactive protein (mg/dL)	211		69		144		15	
Mean ± SD		5.0 ± 6.5		13.2 ± 12.6		12.5 ± 10.0		
Median (IQR)		2.9 (1.0-5.9)		8.3 (3.5-19.3)		8.6 (5.4-18.7)		11.2 (4.9-20.4)
95th percentile		19.9		39.2		34.3		
Reference range ^a		0-1		0-1		0-1		
Procalcitonin (ng/mL)	22		45		71		11	
Mean ± SD		5.7 ± 22.6		8.3 ± 24.5		12.5 ± 26.3		
Median (IQR)		0.11 (0.04-1.66)		1.1 (0.2-6.5)		3.0 (0.5-11.3)		1.02 (0.17-2.93)
95th percentile		91.4		29.1		63.9		
Reference range		<0.11		<0.11		<0.11		
Erythrocyte sedimentation rate (mm/hr)	157		42		91		10	
Mean ± SD		23.5 ± 21.5		59.8 ± 33.8		53.8 ± 29.3		
Median (IQR)		15.0 (8.0-33.0)		68.5 (24.5-96.5)		55.0 (32.0-76.0)		55 (22-58)
95th percentile		75.2		101.0		101.0		
Reference range		0-20		0-20		0-20		
Ferritin (ng/mL) ^b	2		15		36		15	
Mean ± SD		33.7 ± 19.2		138.1 ± 167.4		141.8 ± 161.5		
Median (IQR)		33.7 (20.1-47.3)		120.0 (37.0-139.0)		102.0 (50.2-168.8)		538.4 (253.0-1293.5)
95th percentile		N/A		N/A		513.7		
Reference range		10-70		10-70		10-70		
BNP (pg/mL) ^c	3		10		37		16	
Mean ± SD		1090.0 ± 1367.1		1100.5 ± 2208.9		793.1 ± 1427.2		Elevated in 6/16 patients
Median (IQR)		447.0 (163.0-2660.0)		168.0 (33.0-1039.3)		331.0 (107.0-614.5)		
95th percentile		N/A		N/A		5242.0		
Reference range		<300		<300		<300		
D-Dimer (ug/mL)	6		17		36			
Mean ± SD		1.6 ± 0.8		1.7 ± 1.6		1.8 ± 1.3		Elevated in 12/16 patients
Median (IQR)		1.5 (0.8-2.3)		1.3 (0.8-2.1)		1.5 (0.8-2.5)		
95th percentile		N/A		N/A		4.6		
Reference range		<0.5		<0.5		<0.5		
Troponin (ng/mL)	5		22		49			
Mean ± SD		0.006 ± 0.014		0.003 ± 0.009		0.003 ± 0.011		Elevated in 2/16 patients
Median (IQR)		0.0 (0.0-0.016)		0.0 (0.0-0.0)		0.0 (0.0-0.0)		
95th percentile		N/A		0.03		0.03		
Reference range		<0.035		<0.035		<0.035		

Abbreviations: IQR, interquartile range; UTI = urinary tract infection; BNP, N-terminal pro-B-type natriuretic peptide; N/A, not applicable; MIS-C, multisystem inflammatory syndrome in children

^aReference ranges were obtained from our laboratory reference ranges reported in the electronic medical record. There may be slight variation based on age. The highest range was used.

^bFerritin (n=2): 20.1 ng/mL and 47.3 ng/mL

^cBNP (n=3): 163 pg/mL, 447 pg/mL, and 2660 pg/mL.

historically common bacterial infections, and because expected ranges for many of these inflammatory markers in children with bacterial illnesses are unknown, interpretation was difficult.

To address this knowledge gap, we describe the values of several inflammatory markers observed in hospitalized pediatric patients with selected bacterial infections to assist clinical decision-making if clinicians are again faced with diagnostic ambiguity in the setting of emerging disease processes.

METHODS

A retrospective cohort study was conducted at a tertiary, freestanding children's hospital in the Midwest from March 2018 through

April 2023. Patients > 60 days to 21 years who were discharged from the hospital medicine service with cellulitis, CAP, or UTI were included. Patients with MIS-C or a similar inflammatory syndrome were excluded. Laboratory values and reference ranges were extracted from the electronic health record (Epic Corp). Labs included CRP, procalcitonin, ESR, ferritin, BNP, D-dimer, and troponin. If multiple laboratory values were obtained during admission, only the first value was used for analysis. Data were reported as mean ± standard deviation (SD), median (interquartile range [IQR]), and 95th percentile. The Institutional Review Board at our institution waived the need for ethics approval and patient consent for the collection, analysis, and publication of the

retrospectively obtained and anonymized data for this noninterventional study.

RESULTS

A total of 973 patients were included: 403 with cellulitis, 158 with CAP, and 412 with UTI. Median (IQR) age was 5.6 years (1.9–12.2); 61% were female. The median (IQR) D-dimer (mg/dL) was 1.5 (0.8–2.3) in cellulitis, 1.3 (0.8–2.1) in CAP, and 1.5 (0.8–2.5) in UTI. The median ferritin (ng/mL) was 33.7 (20.1–47.3) in cellulitis, 120.0 (37.0–139.0) in CAP, and 102.0 (50.2–168.8) in UTI. BNP (pg/mL) demonstrated wider ranges, with a median value of 447 (163.0–2660.0) in cellulitis, 168.0 (33.0–1039.3) in CAP, and 331.0 (107.0–614.5) in UTI. Troponin levels were within the reference range for all diagnoses (Table 1).

DISCUSSION

Hospitalized pediatric patients with UTI, CAP, and cellulitis frequently demonstrated elevations in multiple inflammatory markers, making it difficult to differentiate these infections from other inflammatory syndromes such as MIS-C using laboratory evaluation alone. Prior literature suggests that elevated troponin levels occur more frequently in patients with MIS-C.^{1,2} Because cardiac inflammation and myocardial dysfunction are not typically associated with the infections we evaluated, troponin may be a helpful differentiator between these conditions.^{1,2}

As the rest of the observed inflammatory markers are nonspecifically elevated across multiple conditions, utilizing data cutoff points may be of greater diagnostic utility when clinicians are uncertain how to interpret elevated values, although expected ranges for many of these tests remain poorly defined. Prior literature suggested a ferritin level of 228 ng/mL as a cutoff to differentiate patients with and without MIS-C, and our data support this finding, as ferritin levels in our cohort generally remained below this threshold.² Similar laboratory thresholds have not been proposed for other inflammatory markers; however, we observed that the median BNP in our patients was similar to that reported in MIS-C, whereas the median D-dimer was lower than values observed in patients with MIS-C.^{1,2}

Establishing cutoffs for these laboratory tests in pediatric patients may also play a role in future risk stratification. In critically ill pediatric populations, elevated ferritin, BNP, and D-dimer levels have been associated with increased morbidity and mortality, and some of these biomarkers have demonstrated diagnostic utility in selected infections.³⁻⁶ Further research is needed to optimize the clinical utility of these IMs in hospitalized pediatric patients. Such work is important to support diagnostic stewardship and high-value care by promoting judicious test use, accurate interpretation, and informed clinical decision-making.

Strengths of this project include a study design that is easily reproducible at other institutions, allowing expansion of these data in future studies. Limitations include the small sample size, limited

range of infections represented, and retrospective design. Patients were not stratified by illness severity or the presence of cardiac complications. Further research is needed to better understand expected laboratory ranges of less commonly obtained inflammatory markers in hospitalized children to enhance clinical guidance and care delivery.

Financial disclosures: Kelly Graff is a consultant for and receives research support from BioFire Diagnostics, LLC; this company did not participate in this work.

Funding/support: Statistician time for this work was supported by the Medical College of Wisconsin Department of Pediatrics.

Acknowledgements: The authors wish to acknowledge Kelsey Porada, MA, for assistance with institutional review board submission and data formatting.

REFERENCES

1. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: Version 1. *Arthritis Rheumatol*. 2020;72(11):1791-1805. doi:10.1002/art.41454
2. Campbell JI, Roberts JE, Dubois M, Naureckas Li C, Sandora TJ, Lamb GS. Non-SARS-CoV-2 infections among patients evaluated for MIS-C associated with COVID-19. *Pediatr Infect Dis J*. 2021;40(2):e90-e93. doi:10.1097/INF.0000000000002977
3. Valerie IC, Prabandari AASM, Wati DK. Ferritin in pediatric critical illness: a scoping review. *Clin Exp Pediatr*. 2023;66(3):98-109. doi:10.3345/cep.2022.00654
4. Wu JR, Chen IC, Dai ZK, Hung JF, Hsu JH. Early elevated B-type natriuretic peptide levels are associated with cardiac dysfunction and poor clinical outcome in pediatric septic patients. *Acta Cardiol Sin*. 2015;31(6):485-493. doi:10.6515/acs20141201e
5. Wang G, Liu J, Xu R, Liu X. Elevated plasma D-dimer levels are associated with the poor prognosis of critically ill children. *Front Pediatr*. 2022;10:1001893. doi:10.3389/fped.2022.1001893
6. Lee JW, Her SM, Kim JH, et al. D-dimer as a marker of acute pyelonephritis in infants younger than 24 months with urinary tract infection. *Pediatr Nephrol*. 2018;33(4):631-637. doi:10.1007/s00467-017-3843-9

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 2379-3961) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

© 2026 Board of Regents of the University of Wisconsin System and The Medical College of Wisconsin, Inc.

Visit www.wmjonline.org to learn more.