RESEARCH ARTICLE

Variation in Early Inflammatory Marker Testing for Infection-Related Hospitalizations in Children

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ABSTRACT

BACKGROUND AND OBJECTIVES: Inflammatory marker testing in children has been identified as a potential area of overuse. We sought to describe variation in early inflammatory marker (C-reactive protein and erythrocyte sedimentation rate) testing for infection-related hospitalizations across children's hospitals and to determine its association with length of stay (LOS), 30-day readmission rate, and cost.

METHODS: We conducted a cross-sectional study of children aged 0 to 17 years with infection-related hospitalizations using the Pediatric Health Information System. After adjusting for patient characteristics, we examined rates of inflammatory marker testing (C-reactive protein or erythrocyte sedimentation rate) during the first 2 days of hospitalization. We used k-means clustering to assign each hospital to 1 of 3 groups on the basis of similarities in adjusted diagnostic testing rates across 12 infectious conditions. Multivariable regression was used to examine the association between hospital testing group and outcomes.

RESULTS: We included 55 771 hospitalizations from 48 hospitals. In 7945 (14.3%), there was inflammatory marker testing in the first 2 days of hospitalization. We observed wide variation in inflammatory marker testing rates across hospitals and infections. Group A hospitals tended to perform more tests than group B or C hospitals (37.4% vs 18.0% vs 10.4%; $P < .001$) and had the longest adjusted LOS (3.2 vs 2.9 vs 2.8 days; $P = .01$). There was no significant difference in adjusted 30-day readmission rates or costs.

CONCLUSIONS: Inflammatory marker testing varied widely across hospitals. Hospitals with higher inflammatory testing for one infection tend to test more frequently for other infections and have longer LOS, suggesting opportunities for diagnostic stewardship.

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An estimated 4 to 5 billion tests are performed in the United States annually, including many that are essential to the delivery of high-quality health care and a substantial proportion that are unnecessary.[1–4] Routine diagnostic testing and nontargeted testing contribute to the ∼34% of all health care spending in the United States that is attributed to waste.[5] The costs associated with unnecessary testing are not limited to the direct financial burden of the tests on the health care system, but extend to include the psychological costs (eg, anxiety, stress, pain) that patients and their families experience in association with phlebotomy as well as false-positive testing.[6–8] Overuse of diagnostic testing may also lead to downstream consequences, including repeat or expanded testing, the use of unnecessary therapies, prolonged hospitalization, and increased out-of-pocket expenditures of patients and their families.[9,10]

Recently, efforts such as the Choosing Wisely initiative have been focused on improving diagnostic stewardship as a means of improving health care value and curbing health care expenditures. Inflammatory markers (including C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) are obtained in the management of infections and other inflammatory conditions to guide the differentiation of viral from bacterial disease, to tailor antibiotic therapy (including transitions from parenteral to enteral antibiotic therapy), and to determine the length of therapy.[11–16] Although targeted inflammatory marker testing may have the benefit of reducing a proportion of antibiotic overuse and tailoring therapies, widespread nontargeted testing has the potential to promote diagnostic overuse with little added clinical benefit.[17] This is particularly true for concomitant testing given the overlap in information provided between CRP and ESR, both revealing acute inflammation over different time courses. For this reason, the American Society of Clinical Pathology, in one of its Choosing Wisely recommendations, suggests CRP testing over ESR testing, especially when a diagnosis has not yet been established.[18]

Little is known about patterns of use of inflammatory markers and their impact on hospital outcomes across infectious diagnoses in children. Understanding patterns of inflammatory marker testing may identify opportunities to curb unnecessary diagnostic testing in children. Therefore, we sought to describe variation in early inflammatory marker (CRP and ESR) testing across children's hospitals and to determine if variation in testing is associated with hospital resource use, including length of stay (LOS), 30-day readmission rate, and cost.

METHODS

Study Design and Data Source

In this multicenter cross-sectional study of children with an infection-related hospitalization (inpatient and observation), we used the Pediatric Health Information System (PHIS). PHIS is an administrative and billing database of 51 freestanding tertiary care pediatric hospitals in the United States that are affiliated with the Children's Hospital Association (Lenexa, KS). Patient data are deidentified in PHIS; encryption of patient identifiers, however, allows for tracking of individual patients across multiple hospital visits. The current study included data from a total of 48 hospitals, with 3 hospitals excluded for incomplete data. Because we used deidentified data, this study was not considered human subjects research by the policies of the local institutional review board.

Study Population: Inclusion and Exclusion Criteria

Children 0 to 17 years of age with an index hospitalization for infection at a PHIS-participating hospital from January 1, 2016, to December 31, 2017, were eligible for inclusion. Hospitalizations for infection were identified by using All Patient Refined Diagnosis-Related Groups (APR-DRGs) version 32 (3M Corporation, St Paul, MN). APR-DRGs are a patient classification scheme that groups medical patients on the basis of the principal diagnosis and incorporates severity of illness and risk of mortality using demographics and comorbidities. Although originally designed for inpatient stays, the PHIS database uses the APR-DRG grouper for both inpatient and observation stays because dedicated observation units are infrequent in pediatrics and observation stays are defined retrospectively by payer. We examined the following APR-DRG categories: infections of the upper respiratory tract (APR-DRG 113); major respiratory infections and inflammations (APR-DRG 137); bronchiolitis and respiratory syncytial virus (RSV) pneumonia (APR-DRG 138); pneumonia (APR-DRG 139); major gastrointestinal and peritoneal infections (APR-DRG 248); nonbacterial gastroenteritis (APR-DRG 249); osteomyelitis, septic arthritis, and other musculoskeletal infections (APR-DRG 344); cellulitis and other bacterial skin infections (APR-DRG 383); kidney and urinary tract infections (APR-DRG 463); postoperative, posttraumatic, and other device infections (APR-DRG 721); viral illness (APR-DRG 723); and other infectious and parasitic diseases (APR-DRG 724).

We excluded transfers in because of the potential inability to capture diagnostic test use from the transferring hospital. Finally, we excluded patients with cancer and immunodeficiency using Feudtner's complex chronic conditions (CCCs)[19] as well as hospitalizations that included ICU stays because these children may have more complicated infections and because patterns of usage of inflammatory markers may differ from those seen on general inpatient teams. Children within other CCC categories were retained within analyses.

Inflammatory Marker Testing

Inflammatory marker testing was defined as obtaining either a ESR or CRP test. We focused on early testing, defined as during the first 2 days of the hospitalization, because we sought to capture early (emergency department or inpatient) test use across a broad range of infections rather than examine the impact of late or repeat testing on hospitalization outcomes. We chose to examine early testing because a previous study of diagnostic testing revealed that overuse occurred more frequently during initial testing compared with repeat testing.[4] Additionally, this mitigated the risk of identifying a

misleading effect-cause relationship because it would be challenging to determine if children who stay longer have more opportunities to get testing versus testing having a causal role in prolonged LOS. We describe both overall (ie, all PHIS hospitals) and individual hospital testing rates. Concomitant testing was defined as receipt of ESR and CRP tests during the first 2 days of the hospitalization.

Main Outcome Measure

Outcomes included variation in rates of inflammatory marker testing across hospitals. We also examined hospital-level LOS measured in days, all-cause 30-day hospital readmissions, and cost in US dollars. The time frame of 30 days was chosen to measure subsequent visits associated with treatment failure, antibiotic-associated adverse effects, or invasive bacterial infection. Cost of the index hospitalization included use from the emergency department visit and hospitalization. In PHIS, costs are estimated from charges by using hospital year–specific cost-to-charge ratios.

Patient Characteristics

We examined demographic characteristics, including age, sex, race and/or ethnicity, and primary payer. We examined patient characteristics, including the number and types of medical complexity using CCCs.

Statistical Analysis

We calculated unadjusted hospital-level inflammatory marker testing rates for individual infection APR-DRGs. We then adjusted testing rates for age, presence of a CCC, and severity using generalized linear models, controlling for clustering of patients within a hospital using a random intercept for each hospital. For generation of the heat maps, we grouped each hospital by quartile on the basis of adjusted tested rates across each infection APR-DRG. To group hospitals with similar inflammatory marker testing rates, we used k-means clustering, assigning each hospital to 1 of 3 groups on the basis of similarities in adjusted diagnostic testing rates across infection APR-DRGs.[20] Canonical discriminant analysis was used to determine the number of groups. We used descriptive statistics to describe patient and hospital characteristics overall and for each of the 3 testing groups. Comparisons in patient and hospital characteristics across hospital testing groups were conducted by using the Kruskal-Wallis test. Generalized linear mixed models were used to examine the association of hospital testing group and outcomes, with adjustment for age, presence of a CCC, and severity. Severity was defined by using hospitalization resource intensity scores for kids (H-RISKs),[21] which was developed to quantify severity of illness among hospitalized children and used to assign relative weights to each APR-DRG and severity-of-illness level, facilitating comparison across APR-DRG groups. All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc, Cary, NC), and P values $<.05$ were considered statistically significant.

RESULTS

We included 55 771 hospitalizations for infection from 48 hospitals (Table 1). In 7945 (14.2%), inflammatory marker testing was obtained in the first 2 days of hospitalization. The median age was 1 year (interquartile range [IQR] 0–6 years). A majority of patients were male and non-Hispanic white and had government insurance. Approximately 22% of patients had a comorbid CCC. CRP testing rates varied from 2.4% for bronchiolitis and RSV pneumonia to 57.7% for osteomyelitis, septic arthritis, and other musculoskeletal infections. ESR testing rates varied from 0.4% for bronchiolitis and RSV pneumonia to 50.4% for osteomyelitis, septic arthritis, and other musculoskeletal infections. Among patients with a CRP test, ~45.9% also had an ESR test obtained (ie, concomitant testing of ESR and CRP), with the greatest rates of concomitant testing occurring for osteomyelitis, septic arthritis, and other musculoskeletal infections (84.4%), followed by major gastrointestinal and peritoneal infections (56.1%) (Supplemental Table 3). The median unadjusted LOS across hospitals was 2.0 (IQR 1.7–2.2) days, the median unadjusted 30-day all-cause readmission rate across hospitals was 7.3% (IQR 5.8%–8.8%), and the median unadjusted cost across hospitals was $2822 (IQR $1486–$5530).

Variation in Diagnostic Testing

We observed substantial variation in diagnostic testing across hospitals (Fig 1). Hospitals that obtained inflammatory marker testing frequently for one infection appear to test more frequently for other infections. For example, 6 hospitals tested above the median in all 12 diagnosis groups, and 12 hospitals tested below the median in all 12 diagnosis groups. Hospitals that tested more often for CRP also tested more often for ESR across infection subtypes. We observed similar patterns when examining concomitant testing (ie, hospitals that obtained concomitant testing for one infection appeared to obtain concomitant testing for other infections) (Supplemental Fig 3).

Hospital Clustering and Association With Hospital Outcomes

Using k-means clustering, we grouped hospitals into 1 of 3 groups (labeled A for the highest-testing hospitals, B for the moderate-testing hospitals, and C for low-testing hospitals) on the basis of similarities in adjusted diagnostic testing rates. The groups were composed of 6, 13, and 29 hospitals, respectively. Group A hospitals tended to perform more inflammatory marker (CRP or ESR) tests than hospitals in groups B and C (37.4% vs 18.0% vs 10.4%; $P < .001$) (Table 1, Fig 2). Although infants 0 to 1 month of age are frequently considered a distinct population regarding testing practices, differences in the proportions of inflammatory marker tests by group were similarly observed for these infants (Groups A–C: 19.4% vs 10.8% vs 5.9%; $P < .001$). We observed statistically significant but small differences across cluster groups in the distribution of patient demographic and clinical characteristics, such as age, race and/or ethnicity, payer, number and type of chronic conditions, and mean H-RISK (Table 1). Within our adjusted models, we observed a significant difference in mean LOS across testing groups. The hospitals in the highest-testing group (A) had longer adjusted LOS compared with hospitals in groups B and C

TABLE 1 Demographic and Clinical Characteristics Overall and by Hospital Testing Cluster

	Overall	Hospital Cluster Group			*P*
		A	B	C	
No. hospitals	48	6	13	29	—
No. hospitalizations	55 771	3389	16 371	36 011	—
CRP and/or ESR testing, *n* (%)					
CRP	7692 (13.8)	1177 (34.7)	2891 (17.7)	3624 (10.1)	<.001
ESR	3780 (6.8)	634 (18.7)	1178 (7.2)	1968 (5.5)	<.001
CRP or ESR	7945 (14.2)	1266 (37.4)	2950 (18.0)	3729 (10.4)	<.001
CRP and ESR	3527 (6.3)	545 (16.1)	1119 (6.8)	1863 (5.2)	<.001
Sex, *n* (%)					
Female	25 338 (45.4)	1553 (45.8)	7345 (44.9)	16 440 (45.7)	.219
Male	30 433 (54.6)	1836 (54.2)	9026 (55.1)	19 571 (54.3)	—
Age, y, *n* (%)					
<1	18 995 (34.1)	1017 (30.0)	5392 (32.9)	12 586 (35.0)	<.001
1–5	21 589 (38.7)	1231 (36.3)	6578 (40.2)	13 780 (38.3)	—
6–12	9354 (16.8)	700 (20.7)	2716 (16.6)	5938 (16.5)	—
13–17	5833 (10.5)	441 (13.0)	1685 (10.3)	3707 (10.3)	—
Race and/or ethnicity, *n* (%)					
Non-Hispanic white	27 407 (49.1)	1477 (43.6)	6483 (39.6)	19 447 (54.0)	<0001
Non-Hispanic Black	7540 (13.5)	356 (10.5)	1694 (10.3)	5490 (15.2)	—
Hispanic	12 063 (21.6)	932 (27.5)	5303 (32.4)	5828 (16.2)	—
Asian	1095 (2.0)	79 (2.3)	410 (2.5)	606 (1.7)	—
Other	7666 (13.7)	545 (16.1)	2481 (15.2)	4640 (12.9)	—
Payer, *n* (%)					
Private	20 378 (36.5)	1284 (37.9)	5668 (34.6)	13 426 (37.3)	<.001
Government	33 398 (59.9)	1947 (57.5)	10 291 (62.9)	21 160 (58.8)	—
Other	1995 (3.6)	158 (4.7)	412 (2.5)	1425 (4.0)	—
Chronic conditions, *n* (%)					
Any chronic condition	11 984 (21.5)	758 (22.4)	3368 (20.6)	7858 (21.8)	.002
Cardiovascular	2555 (4.6)	143 (4.2)	748 (4.6)	1664 (4.6)	.563
Neurologic and neuromuscular	2652 (4.8)	145 (4.3)	736 (4.5)	1771 (4.9)	.044
Respiratory	1368 (2.5)	82 (2.4)	356 (2.2)	930 (2.6)	.020
Renal and urologic	1917 (3.4)	125 (3.7)	470 (2.9)	1322 (3.7)	<.001
Gastrointestinal	4700 (8.4)	285 (8.4)	1310 (8.0)	3105 (8.6)	.060
Hematology and immunodeficiency	1610 (2.9)	113 (3.3)	465 (2.8)	1032 (2.9)	.272
Metabolic	1530 (2.7)	80 (2.4)	442 (2.7)	1008 (2.8)	.302
Other congenital or genetic defect	2221 (4)	133 (3.9)	664 (4.1)	1424 (4.0)	.846
Neonatal	510 (0.9)	27 (0.8)	154 (0.9)	329 (0.9)	.725
Technology dependency	4828 (8.7)	277 (8.2)	1327 (8.1)	3224 (9.0)	.004
Transplantation	70 (0.1)	3 (0.1)	19 (0.1)	48 (0.1)	.719
No. CCCs, *n* (%)					
No CCCs	43 787 (78.5)	2631 (77.6)	13 003 (79.4)	28 153 (78.2)	.001
1 CCC	5880 (10.5)	402 (11.9)	1686 (10.3)	3792 (10.5)	—
2 CCCs	2416 (4.3)	151 (4.5)	649 (4.0)	1616 (4.5)	—
3+ CCCs	3688 (6.6)	205 (6.0)	1033 (6.3)	2450 (6.8)	—
Mean H-RISK (SD)	0.355 (0.276)	0.373 (0.284)	0.361 (0.291)	0.351 (0.269)	<.001

Hospitals in group A are high-testing hospitals, those in group B are intermediate-testing hospitals, and those in group C are low-testing hospitals. —, not applicable.

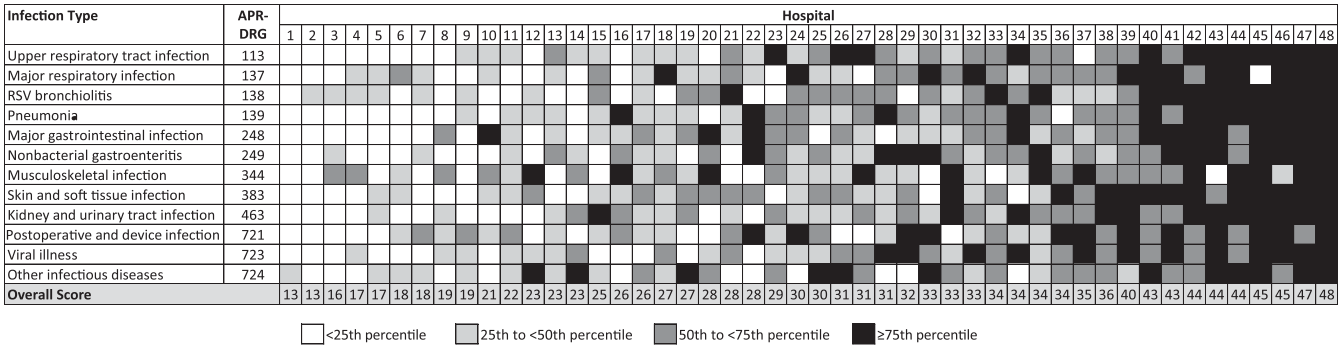

FIGURE 1 Heat map of adjusted inflammatory marker testing rate quartiles across hospitals. Within the heat map, each quartile was assigned a score of 1 to 4, with scores summed across infection types within a hospital. Data are sorted on the basis of the overall score for each hospital. Hospitals with lower overall scores are presented on the left, and those with higher overall scores are presented on the right. Data are adjusted for age, presence of CCCs, and severity by using H-RISK.

(3.24 vs 2.85 vs 2.82 days; $P < .01$) (Table 2). There was no significant difference in adjusted mean 30-day readmission rates or costs.

DISCUSSION

In this multicenter cross-sectional study of early inflammatory marker testing in children, we observed wide variation in inflammatory marker use in children hospitalized with infections. We identified 2 major findings: (1) hospitals that obtained early inflammatory marker testing frequently for one infection obtained early inflammatory marker testing more frequently for other infections, and (2) hospitals with greater early inflammatory marker testing had longer LOS without a significant effect in readmission rates. These findings suggest opportunities to promote diagnostic stewardship.

As expected in our current study, inflammatory marker testing varied widely across infections. Although inflammatory markers were obtained infrequently for bronchiolitis (consistent with guidelines[22]), they were obtained with greater frequency for other infections, such as osteomyelitis, septic arthritis, and other musculoskeletal infections, in which studies have clearly defined evidence-based recommendations for use of inflammatory markers in diagnosing (eg, Kocher criteria[23]) and guiding antibiotic therapy, including transitions to oral antibiotics. Inflammatory markers are used to assist in the diagnosis and management of infections and inflammatory conditions as well as to promote antimicrobial stewardship and reduce unnecessary exposure to antibiotics.[14,24,25] However, because CRP and ESR testing lack sensitivity and specificity, their utility in assisting with diagnosis lies primarily in cases in which there is either high or low pretest probability of a bacterial

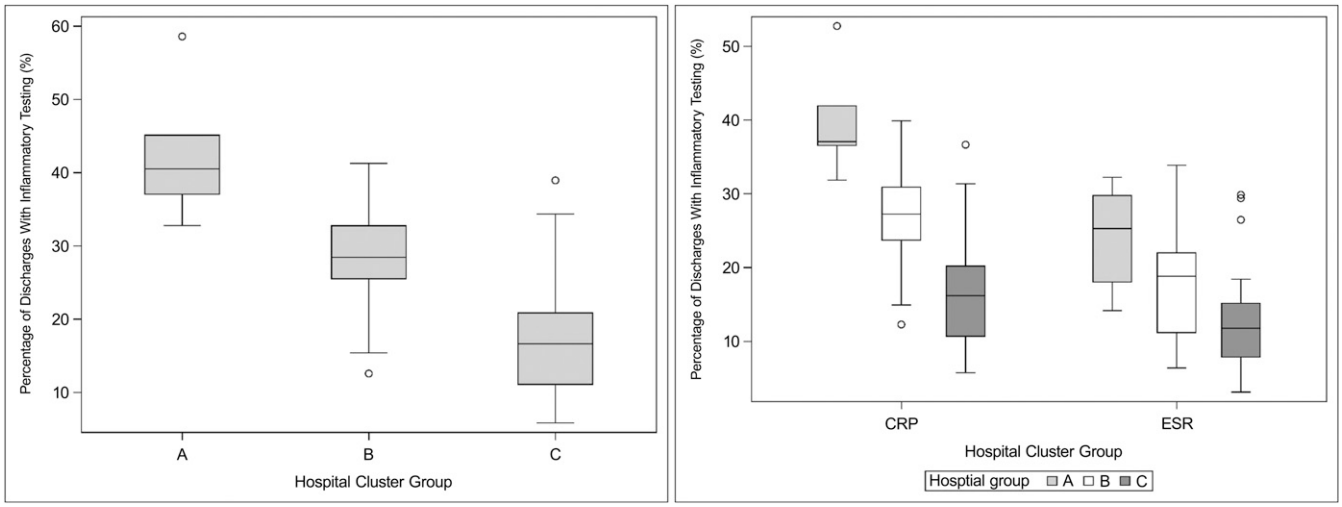

FIGURE 2 Box and whisker diagrams revealing unadjusted percentage of inflammatory testing and interquartile ranges within testing clusters. Hospitals in group A are high-testing hospitals, those in group B are intermediate-testing hospitals, and those in group C are low-testing hospitals.

TABLE 2 Association of Hospital Testing Clusters and Outcomes (LOS, 30-Day Readmissions, and Cost)

	Hospital Cluster Group			*P*
	A	B	C	
LOS, d, mean (95% CI)	3.24 (2.97–3.54)	2.85 (2.68–3.02)	2.82 (2.71–2.93)	.013
30-Day readmission rate, %, mean (95% CI)	10.8 (8.7–13.2)	9.3 (8.0–10.7)	10.1 (9.1–11.2)	.426
Cost, $, mean (95% CI)	7766 (5693–10 594)	6270 (5077–7744)	5538 (4806–6381)	.131

Data are adjusted for age, presence of CCCs, and severity by using H-RISK. Hospitals in group A are high-testing hospitals, those in group B are intermediate-testing hospitals, and those in group C are low-testing hospitals. CI, confidence interval.

infection. Although diagnostic testing may help clinicians to exclude bacterial illnesses (ie, reduce antibiotic prescriptions) or transition to oral antibiotics sooner (ie, reduce exposure to parenteral antibiotics), overreliance on routine inflammatory marker testing may contribute to increased health care use and costs. For example, Kainth and Gigliotti[17] previously reported that concomitant ESR and CRP testing within a large academic center resulted in increased expenditures without substantial clinical benefit. In other studies, authors describe a cascade effect, with practitioners obtaining increased rates of consultations, tests, and referrals in the setting of false-positive inflammatory marker testing.[26] Consequently, in future studies, researchers should seek to define best practices for inflammatory marker testing and investigate strategies that balance diagnostic stewardship with antimicrobial stewardship to tackle health care spending.

Our current study highlights how several hospitals with increased inflammatory marker testing for one infectious diagnosis tend to have increased inflammatory marker testing for other infectious diagnoses, including increased rates of concomitant testing. Although variation in testing across conditions is desirable (ie, variation based on differential evidence), substantial variation in adjusted testing rates across hospitals is perhaps more worrisome and highlights an opportunity to standardize aspects of care across institutions, especially where these differences are associated with differences in hospitalization outcomes (eg, increased LOS). The reasons behind increased intensity of testing at some hospitals are likely numerous and include both individual provider factors, such as provider experience, practicing defensive medicine, and low tolerance of diagnostic ambiguity, as well as systems factors.[27] Systems factors, such as local testing culture, may impact diagnostic test use at an organizational level and contribute to patterns in overuse similar to that observed in our study. For example, local protocols and/or policies, driven by factors such as the training environment or the intensity of services hospital wide (eg, more oncology patients or patients with immunodeficiency with limited ability to mount a fever response), may influence testing patterns at individual institutions. These results highlight that in addition to addressing individual testing behaviors, future interventions to impact diagnostic test use should also address testing culture within health care systems.[28]

In our study, increased inflammatory marker testing was associated with increased LOS, without concomitant reductions in 30-day readmissions or association with costs. This finding is consistent with a growing body of literature revealing that variation in testing is associated with increased health care use.[29–31] Although differences in LOS in adjusted analyses were modest in our study (ie, $<$12 hours), one cannot underestimate the impact that improving LOS can have on patients, families, and health care systems. For example, reducing LOS may help alleviate some of the emotional and financial stress that patients and their families experience, even for hospitalizations for transient illnesses, while simultaneously reducing an individual patient's risk of obtaining false-positive results that require additional follow-up.[32–38] Additionally, reducing LOS can improve hospital efficiency and may potentially lead to cost savings.[39] Our observation of no statistical differences in readmissions and cost is not wholly unexpected. Readmissions are overall uncommon in children, and although costs did decrease in a relatively linear manner across high- to low-testing institutions, these differences were not statistically significant. Our findings for costs likely reflect the fact that LOS is the predominant driver of pediatric inpatient costs and that institutional intensity of testing and services is more likely to influence LOS compared with cost. Taken together, our findings further suggest that increased resource use is not synonymous with improved health care delivery and that there are opportunities to reduce inflammatory marker testing, including reducing rates of concomitant testing.

Efforts such as the Choosing Wisely campaign have led to enhanced recognition of diagnostic overuse and initiation of local and national quality improvement initiatives aimed at reducing overuse. Recent studies reveal that implementation of quality improvement methodology and clinical practice guidelines may encourage reductions in unnecessary diagnostic testing. For example, use of quality improvement initiatives, such as education and standardized communication, has led to reductions in electrolyte and complete blood cell count testing as well as reductions in chest radiography for asthma.[40–42] Similarly, use of clinical practice guidelines has effectively lead to reductions in unnecessary bronchodilator, antibiotic, and chest radiography use in pediatric bronchiolitis.[43,44] Although future studies are needed to define best practices for inflammatory marker testing and to outline achievable benchmarks for testing, use of quality improvement methodology and clinical practice guidelines may be effective strategies to reduce unnecessary inflammatory marker testing.

Our study should be interpreted in the context of several limitations. First, the PHIS

database is an administrative database and does not contain data pertaining to clinical decision-making surrounding diagnostic testing. Consequently, we are limited in our ability to evaluate the appropriateness of diagnostic testing (ie, to determine if diagnostic test obtainment truly impacted the decision to start an antibiotic or the decision of when to transition to oral therapy). Additionally, we are unable to examine how local protocols and/or policies influence testing patterns at individual institutions because these data are not collected by PHIS. We sought to broadly describe variation in inflammatory marker use; however, procalcitonin testing was obtained infrequently across PHIS-participating hospitals during our study period and was not included in the analyses despite its demonstrated improved sensitivity and specificity compared with CRP testing for identifying febrile infants.[45,46] Although we accounted for factors such as age, presence of a complex chronic condition, and APR-DRG severity of illness in our analyses, unaccounted-for differences in patient characteristics could certainly have contributed to variation and observed differences in the relationship between test variation and hospitalization outcomes across groups. Our focus on variation in initial testing during the first 2 days of hospitalization was only one aspect of pediatric diagnostic test overuse, and in future evaluations, researchers should focus on examining the impact of repeat diagnostic test obtainment on hospitalization outcomes.

CONCLUSIONS

For children hospitalized with infection, inflammatory marker testing varies widely across infection types and hospitals. Hospitals with higher inflammatory testing for one infection tend to test more frequently across other infection diagnoses and have longer LOS, suggesting a culture of overuse at some hospitals. Our results highlight the need to define best practices for diagnostic test use and the need for future quality improvement initiatives centered on optimizing diagnostic stewardship processes to improve health care value.

REFERENCES

1. Bruce Alexander C. Message from the president: reducing healthcare costs through appropriate test utilization. *Critical Values*. 2012;5(2):6–9
2. Miyakis S, Karamanof G, Liontos M, Mountokalakis TD. Factors contributing to inappropriate ordering of tests in an academic medical department and the effect of an educational feedback strategy. *Postgrad Med J*. 2006;82(974): 823–829
3. Rehmani R, Amanullah S. Analysis of blood tests in the emergency department of a tertiary care hospital. *Postgrad Med J*. 1999;75(889): 662–666
4. Zhi M, Ding EL, Theisen-Toupal J, Whelan J, Arnaout R. The landscape of inappropriate laboratory testing: a 15-year meta-analysis. *PLoS One*. 2013; 8(11):e78962
5. Berwick DM, Hackbarth AD. Eliminating waste in US health care. *JAMA*. 2012; 307(14):1513–1516
6. Bisogni S, Dini C, Olivini N, et al. Perception of venipuncture pain in children suffering from chronic diseases. *BMC Res Notes*. 2014;7:735
7. Postier AC, Eull D, Schulz C, et al. Pain experience in a US children's hospital: a point prevalence survey undertaken after the implementation of a system-wide protocol to eliminate or decrease pain caused by needles. *Hosp Pediatr*. 2018;8(9):515–523
8. Coon ER, Young PC, Quinonez RA, Morgan DJ, Dhruva SS, Schroeder AR. 2017 update on pediatric medical overuse: a review. *JAMA Pediatr*. 2018; 172(5):482–486
9. Brownlee S, Chalkidou K, Doust J, et al. Evidence for overuse of medical services around the world. *Lancet*. 2017; 390(10090):156–168
10. Chua KP, Schwartz AL, Volerman A, Conti RM, Huang ES. Use of low-value pediatric services among the commercially insured. *Pediatrics*. 2016;138(6): e20161809
11. Chou ACC, Mahadev A. The use of C-reactive protein as a guide for transitioning to oral antibiotics in pediatric osteoarticular infections. *J Pediatr Orthop*. 2016;36(2):173–177
12. Arnold JC, Cannavino CR, Ross MK, et al. Acute bacterial osteoarticular infections: eight-year analysis of C-reactive protein for oral step-down therapy. *Pediatrics*. 2012;130(4). Available at: www.pediatrics.org/cgi/content/full/130/4/e821
13. Petel D, Winters N, Gore GC, et al. Use of C-reactive protein to tailor antibiotic use: a systematic review and meta-analysis. *BMJ Open*. 2018;8(12):e022133
14. Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. *Br J Gen Pract*. 2013; 63(616):e787–e794
15. Hoshina T, Nanishi E, Kanno S, Nishio H, Kusuhara K, Hara T. The utility of biomarkers in differentiating bacterial from non-bacterial lower respiratory tract infection in hospitalized children: difference of the diagnostic performance between acute pneumonia and bronchitis. *J Infect Chemother*. 2014; 20(10):616–620
16. Bray C, Bell LN, Liang H, et al. Erythrocyte sedimentation rate and C-reactive protein measurements and their relevance in clinical medicine. *WMJ*. 2016;115(6):317–321
17. Kainth MK, Gigliotti F. Simultaneous testing of erythrocyte sedimentation rate and C-reactive protein: increased expenditure without demonstrable benefit. *J Pediatr*. 2014;165(3):625–627
18. American Society for Clinical Pathology. CRP for acute phase inflammation. Available at: www.choosingwisely.org/clinician-lists/american-society-clinical-pathology-erythrocyte-sedimentation-rate-for-acute-phase-inflammation/. Accessed March 19, 2019
19. Feudtner C, Feinstein JA, Zhong W, Hall M, Dai D. Pediatric complex chronic

conditions classification system version 2: updated for ICD-10 and complex medical technology dependence and transplantation. *BMC Pediatr*. 2014;14:199

20. Thomson J, Hall M, Berry JG, et al. Diagnostic testing and hospital outcomes of children with neurologic impairment and bacterial pneumonia. *J Pediatr*. 2016;178:156–163.e1
21. Richardson T, Rodean J, Harris M, Berry J, Gay JC, Hall M. Development of hospitalization resource intensity scores for kids (H-RISK) and comparison across pediatric populations. *J Hosp Med*. 2018; 13(9):602–608
22. Ralston SL, Lieberthal AS, Meissner HC, et al; American Academy of Pediatrics. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics*. 2014;134(5). Available at: www.pediatrics.org/cgi/content/full/134/5/e1474
23. Kocher MS, Zurakowski D, Kasser JR. Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence-based clinical prediction algorithm. *J Bone Joint Surg Am*. 1999;81(12):1662–1670
24. Bjerrum L, Gahrn-Hansen B, Munck AP. C-reactive protein measurement in general practice may lead to lower antibiotic prescribing for sinusitis. *Br J Gen Pract*. 2004;54(506):659–662
25. Lindström J, Nordeman L, Hagström B. What a difference a CRP makes. A prospective observational study on how point-of-care C-reactive protein testing influences antibiotic prescription for respiratory tract infections in Swedish primary health care. *Scand J Prim Health Care*. 2015;33(4):275–282
26. Watson J, Salisbury C, Whiting P, Banks J, Pyne Y, Hamilton W. Added value and cascade effects of inflammatory marker tests in UK primary care: a cohort study from the Clinical Practice Research Datalink. *Br J Gen Pract*. 2019;69(684): e470–e478
27. Deyo RA. Cascade effects of medical technology. *Annu Rev Public Health*. 2002; 23(1):23–44
28. Gupta R, Moriates C. Swimming upstream: creating a culture of high-value care. *Acad Med*. 2017;92(5):598–601
29. Markham JL, Hall M, Bettenhausen JL, Myers AL, Puls HT, McCulloh RJ. Variation in care and clinical outcomes in children hospitalized with orbital cellulitis. *Hosp Pediatr*. 2018;8(1):28–35
30. Florin TA, French B, Zorc JJ, Alpern ER, Shah SS. Variation in emergency department diagnostic testing and disposition outcomes in pneumonia. *Pediatrics*. 2013;132(2):237–244
31. Lind CH, Hall M, Arnold DH, et al. Variation in diagnostic testing and hospitalization rates in children with acute gastroenteritis. *Hosp Pediatr*. 2016;6(12):714–721
32. Commodari E. Children staying in hospital: a research on psychological stress of caregivers. *Ital J Pediatr*. 2010; 36:40
33. Bevans M, Sternberg EM. Caregiving burden, stress, and health effects among family caregivers of adult cancer patients. *JAMA*. 2012;307(4):398–403
34. El-Jawahri AR, Traeger LN, Kuzmuk K, et al. Quality of life and mood of patients and family caregivers during hospitalization for hematopoietic stem cell transplantation. *Cancer*. 2015;121(6): 951–959
35. Johaningsmeir SA, Colby H, Krauthoefer M, Simpson P, Conceição SCO, Gordon JB. Impact of caring for children with medical complexity and high resource use on family quality of life. *J Pediatr Rehabil Med*. 2015;8(2):75–82
36. Cohen SA, Cook S, Kelley L, Sando T, Bell AE. Psychosocial factors of caregiver burden in child caregivers: results from the new national study of caregiving. *Health Qual Life Outcomes*. 2015;13:120
37. de Oliveira GR, Neto JF, de Camargo SM, Lucchetti ALG, Espinha DCM, Lucchetti G. Caregiving across the lifespan: comparing caregiver burden, mental health, and quality of life. *Psychogeriatrics*. 2015;15(2):123–132
38. Chang LV, Shah AN, Hoefgen ER, et al; H2O Study Group. Lost earnings and nonmedical expenses of pediatric hospitalizations. *Pediatrics*. 2018;142(3): e20180195
39. Health Catalyst. Systematic, data-driven approach lowers length of stay and improves care coordination. Available at: https://www.healthcatalyst.com/success_stories/reducing-length-of-stay-memorial-hospital-at-gulfport. Accessed April 22, 2019
40. Tchou MJ, Tang Girdwood S, Wormser B, et al. Reducing electrolyte testing in hospitalized children by using quality improvement methods. *Pediatrics*. 2018; 141(5):e20173187
41. Johnson DP, Lind C, Parker SES, et al. Toward high-value care: a quality improvement initiative to reduce unnecessary repeat complete blood counts and basic metabolic panels on a pediatric hospitalist service. *Hosp Pediatr*. 2016;6(1):1–8
42. Watnick CS, Arnold DH, Latuska R, O'Connor M, Johnson DP. Successful chest radiograph reduction by using quality improvement methodology for children with asthma. *Pediatrics*. 2018; 142(2):e20174003
43. Breakell R, Thorndyke B, Clennett J, Harkensee C. Reducing unnecessary chest X-rays, antibiotics and bronchodilators through implementation of the NICE bronchiolitis guideline. *Eur J Pediatr*. 2018;177(1): 47–51
44. Genies MC, Kim JM, Pyclik K, Rossi S, Spicyn N, Serwint JR. Impact of an educational intervention to improve physician adherence to bronchiolitis clinical practice guidelines: a pre-post intervention study. *Clin Pediatr (Phila)*. 2018;57(3):253–258
45. Gomez B, Bressan S, Mintegi S, et al. Diagnostic value of procalcitonin in well-appearing young febrile infants. *Pediatrics*. 2012;130(5):815–822
46. 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(1):62–69