Use of C-Reactive Protein and Ferritin Biomarkers in Daily Pediatric Practice

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Practice Gap

Recent reports have detailed the use of these widely available biomarkers in diagnosing and predicting outcomes in a wide array of clinical diseases, most of which are severe, life-threatening, and difficult to diagnose. Many pediatricians have difficulty understanding and using the results of C-reactive protein and ferritin blood tests, which are easily accessible in clinical practice. This summary of the literature can assist in the interpretation and application of these useful and readily available tools in their clinical practice.

Objectives

After completing this article, readers should be able to:

1. Understand the clinical evidence behind the use of C-reactive protein and ferritin biomarkers in clinical practice.
2. Appropriately use these tools and the clinical consensus detailed in the following review to accurately and astutely diagnose severe infection and inflammatory disease.

Abstract

Recent pediatric clinical research has begun to focus on risk stratification tools using multibiomarker models. C-reactive protein (CRP) and ferriti biomarkers are widely available and used to varying degrees in daily practice, but there is no single source examining the evidence behind their use.

We set out to summarize the evidence behind the use of CRP and ferritin biomarkers in pediatric practice and to begin development of a consensus for their future use for pediatricians.

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ABBREVIATIONS

CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
HLH	hemophagocytic lymphohistiocytosis
IL	interleukin
IVIg	intravenous immunoglobulin
MAS	macrophage activation syndrome
MODS	multiple organ dysfunction syndrome
SIRS	systemic inflammatory response syndrome
sJIA	systemic juvenile idiopathic arthritis

All the literature involving CRP and ferritin in pediatrics available on PubMed was surveyed. Research applicable to daily pediatric practice was summarized in the body of the article. Pediatric clinicians of various subspecialties contributed to the summary of the use of CRP and ferritin biomarkers in clinical practice in various disease processes. A clinical decision pathway is described, and evidence is summarized.

CRP and ferritin biomarkers have diverse uses with various cutoff values in the literature, making their use in daily practice difficult. Elevation of these markers coincides with their significant elevation in uncontrolled inflammation.

CRP and ferritin biomarkers are widely used in pediatrics. This review provides a resource summarizing evidence into a single source. There is sufficient evidence to indicate that these biomarkers of inflammation can be useful in guiding clinical decision making in specific clinical scenarios; however, further work is needed to improve their use in clinical practice.

INTRODUCTION

During the past decade, the use of biomarkers in clinical pediatrics has risen steadily. Most recently, the use of risk stratification tools using multibiomarker models has come to the forefront. Examples of these tools include the pediatric sepsis biomarker risk model, (1) the risk stratification model of acute pyelonephritis, (2) and the use of inflammatory biomarkers to predict exacerbations in chronic obstructive pulmonary disease. (3) Clinicians have started using these models to guide treatment decisions, at times choosing more aggressive regimens for those at higher risk. Unfortunately, many of these decision models can be applied only to patients in specific demographic groups, or they use biomarkers not widely tested in clinical laboratories. Although some of these models have proven usefulness, work in other areas has shown variability and nonspecificity in biomarkers, keeping clinical judgment as the mainstay in medical management in these areas. For example, in pediatric acute liver failure, many large studies examining diverse biomarkers with basic outcomes, including transplant and mortality, have shown limited usefulness in biomarkers compared with clinical scales alone. (4) Biomarker models in smaller, more specific cohorts have shown significant value. (5)

Two of the most common and readily available biomarkers in pediatrics are C-reactive protein (CRP) and ferritin. Recent work has examined the use of these biomarkers in conjunction with others, such as erythrocyte sedimentation rate (ESR) and procalcitonin, which are available to varying extents, but these other markers have not been as widely examined and have more specific uses in clinical practice. The present review surveys the literature for current evidence in pediatric practice for the use of CRP and ferritin biomarkers. All the literature involving the use of CRP and ferritin biomarkers in pediatrics available on PubMed was surveyed. *CRP* and *ferritin* were used as primary search terms, in conjunction with the term *pediatrics* and with the areas of the specific subheadings listed herein. Papers were included if there was a significant contribution to current clinical practice. Research that focused on pediatric practice is summarized in the body of this article.

Based on the previously described literature review and a multidisciplinary pediatric specialty group discussion via a survey tool, we describe a clinical systematic summary of evidence for the use of CRP and ferritin as tools in pediatrics (Tables 1 and 2, Fig). Pediatric clinicians of various subspecialties contributed, including specialists in general hospitalist pediatrics, emergency care, intensive care, neonatology, hematology, oncology, bone marrow transplant, gastroenterology, rheumatology, infectious disease, cardiology, pulmonology, nephrology, general pediatric surgery, and pediatric transplant surgery. The findings of the survey are compiled into a clinical decision tool that general pediatricians can use for patients who have CRP levels greater than 40 mg/L (>381 nmol/L) and ferritin levels greater than 1,000 ng/mL (>2,247 pmol/L) (Table 1, Fig).

TABLE 1. **Summary of the Clinical Consensus with Cutoff Values of CRP >40 mg/L (>381 nmol/L) and Ferritin >1,000 ng/mL (>2,247 pmol/L)**

CLINICAL DECISIONS FOR ELEVATED CRP AND FERRITIN LEVELS
Elevated CRP level (>40 mg/L [>381 nmol/L])
CRP interacts with components of bacterial cell walls and the phosphocholine component exposed after cell death. It can be an indicator of bacterial or fungal infection or of necrotic tissue. CRP facilitates complement activation and phagocytosis by macrophages and dendritic cells, initiating an appropriate immune response. It is also commonly elevated with trauma and surgical procedures. Elevation also occurs in diseases with inappropriate inflammation, such as rheumatologic diseases and lymphomas.
Potential course of action
Consider evaluation for infectious sources and following as a sign of response to treatment
If suspected inflammatory bowel disease, may indicate disease flare; initiate appropriate investigation, consider corticosteroids and increased therapy if no response
If suspected pancreatitis, may indicate disease severity
If renal cause suspected, remove central catheters or allograft in transplant patients
If suspected GvHD, exclude alternative or coexisting causes such as infection, may be followed as an indicator of response to treatment
If known systemic lupus erythematosus or juvenile dermatomyositis, suspect infection greater than disease flare if no serositis
Elevated ferritin level (>1,000 ng/mL [>2,247 pmol/L])
Ferritin is another acute-phase protein that can be elevated in chronic iron overload states and can acutely elevate in the presence of macrophage activation. In patients with ferritin levels >1,000 ng/mL (>2,247 pmol/L), there is a significant risk of PICU admission and mortality over 5 years. It is acutely elevated in sJIA, MAS, primary HLH, reactive HLH, and viral infections. Extremely high levels in sepsis associate with mortality and hyperinflammation. It is predictive of outcomes in hematopoietic cell transplant.
Potential course of action
Suspicion for sJIA, HLH, MAS, malignancy, iron overload, also possibly a viral infection or posttransplant lymphoproliferative disease (uncontrolled Epstein-Barr virus proliferation)
Consider chelation or phlebotomy if suspected iron overload
Consider consultation with infectious diseases, hematology/oncology, rheumatology if unexplained inflammatory process
Elevated CRP level (>40 mg/L [>381 nmol/L]) and ferritin level (>1,000 ng/mL [>2,247 pmol/L])
This combination can indicate a severe inflammatory process that should be addressed to prevent impending morbidity
Potential course of action
Consider acute infection or inflammation, especially HLH, MAS (ferritin level >10,000 ng/mL [>22,470 pmol/L])
Consider infectious evaluation, investigation for HLH, treatment for HLH if high clinical suspicion
If multiple organ failure and secondary MAS/HLH (without CNS involvement, not in infancy), consider intravenous immunoglobulin, methylprednisone (dexamethasone if concern for CNS involvement), plasma exchange, anakinra; early consultation with infectious diseases, hematology/oncology, and rheumatology for the next course of action, including diagnostic studies as soon as possible and consideration of treatment
If primary HLH (ferritin level >10,000 ng/mL [>22,470 pmol/L]), indicated by CNS involvement, onset in infancy, consanguinity), consult hematology/oncology/bone marrow transplant for diagnostic evaluation

CNS=central nervous system, CRP=C-reactive protein, GvHD=graft-versus-host disease, HLH=hemophagocytic lymphohistiocytosis, MAS=macrophage activation syndrome, sJIA=systemic juvenile idiopathic arthritis.

CRP ELEVATION

CRP is an acute-phase protein produced in the liver that is involved in the innate immune response. (55) It was the first discovered pattern recognition receptor. (56) CRP has been shown to bind to apoptotic cells, eliminating the cells before necrosis through phagocytosis and preventing immune activation, and to phosphorylcholine in bacterial capsules, promoting clearance of bacterial lysis products, which can cause inflammation, through binding to Fc receptors. (57)(58) Furthermore, it can activate the classical complement

TABLE 2. **Course of Action for Elevated CRP and Ferritin Levels in Various Clinical Scenarios, with Given Cutoff Values Determined from Pooled Literature with Input from a Pediatric Clinical Subspecialty Group**

CLINICAL SCENARIO	COURSE OF ACTION
Fever with elevated CRP level	
New infection/sepsis?	Suspect bacterial infection (CRP level >87 mg/L [>829 nmol/L]) (6)(7) High procalcitonin level, consider antibiotic drug therapy Low procalcitonin level, consider antifungal drug therapy (CRP level >100 mg/L [952 nmol/L]) (8)(9)
Infants with fever?	Suspect bacterial infection (CRP level >50 mg/L [>476 nmol/L] if ill, >200 mg/L [>1,905 nmol/L] if well) (10)(11) High interleukin-6 level, consider antibiotic drug therapy; low interleukin-6 level, consider antifungal drug therapy (12)
Febrile neutropenia?	If low absolute monocyte count, consider fungal infection (CRP level >90 mg/L [>857 nmol/L]) (13) Low interleukin-6 level, consider coverage for fungal infection (CRP level >30 mg/L [>286 nmol/L]) (14) Remains elevated, consider antifungal or second-line antibiotic drug coverage (15)(16)
Osteomyelitis/septic joint?	May be useful in ruling out, combine CRP and ESR for treatment efficacy (CRP level <20 mg/L (<190 nmol/L) for ruling out, CRP level <30 mg/L [<286 nmol/L] for efficacy) (17)(18)
Surgery?	Should decrease over time. If increasing on postoperative day 3, source control of possible infection (CRP level >110 mg/L [>1,048 nmol/L], CRP level >30 mg/L [>286 nmol/L] in appendicitis) (19)(20)(21)(22)
Solid organ transplant?	After postoperative day 5, consider thrombosis, infection, rejection (CRP level >20 mg/L [>190 nmol/L]) (23)
Bone marrow transplant?	Treat GvHD, concern for bacterial or fungal infection (CRP level >43.5 mg/L [>414 nmol/L] for bacteria, CRP level >70.5 mg/L (>671 nmol/L) for fungus indicates increased mortality risk) (24)
Inflammatory bowel disease?	Consider investigation for abscess or other infection and for disease flare Track for response to treatment (CRP level >5 mg/L [>48 nmol/L]) (25)(26)
Juvenile idiopathic arthritis?	Useful in prognosis. Follow for treatment response. Higher levels indicate sJIA (CRP level >50 mg/L [>476 nmol/L] for prognosis) (27)(28)(29)
Kawasaki disease?	Useful in diagnosis and prognosis (CRP level >100 mg/L [>952 nmol/L]). (30)(31)(32) Follow for treatment response and possible retreatment with IVIg (CRP level >80 mg/L [>762 nmol/L]) (33)
Juvenile dermatomyositis?	Concern for infection, no correlation with disease activity (34)
SLE?	Concern for infection, no correlation with disease activity (35)
ICU population?	Associated with mortality, consider aggressive treatments (CRP level >100 mg/L [>952 nmol/L]) (36)
Elevated ferritin level	
Familial hemochromatosis?	Useful for diagnosis, follow for response to chelation/phlebotomy (ferritin level >1,000 ng/mL [>2,247 pmol/L]) (37)(38)(39)(40)(41)
Anemia?	Differentiates chronic hemolytic anemia (thalassemia/sickle cell) Median ferritin level 850 ng/mL (1,910 pmol/L) for thalassemia, 163 ng/mL (366 pmol/L) for sickle cell (42)(43)
Fever?	Consider viral infection, especially Epstein-Barr virus (median ferritin level 431 ng/mL [968 pmol/L]) (44)
Severe sepsis/septic shock?	Associated with mortality (ferritin level >4,420 ng/mL (>9,931 pmol/L), >1,980 ng/mL (>4,449 pmol/L) when combined with CRP level >40.8 mg/L [>389 nmol/L]). (45)(46)(47)
All patients?	Associated with ICU admission and mortality (ferritin level >500 ng/mL [>1,123 pmol/L]) (48)
sJIA?	Concern for MAS, treat with corticosteroids, other agents (ferritin level >500 ng/mL [>1,123 pmol/L]) (49)
SLE?	Concern for MAS, treat with corticosteroids, other agents (ferritin level >500 ng/mL [>1,123 pmol/L]) (50)
Bone marrow transplant?	Correlates with prognosis, consider chelation therapy (ferritin level >300 ng/mL [>674 pmol/L]) (51)(52)(53) Monitor for hepatic veno-occlusive disease, sepsis (ferritin level >1,000 ng/mL [>2,247 pmol/L]) (53)

Continued

TABLE 2. (Continued)

CLINICAL SCENARIO	COURSE OF ACTION
Fever with CRP level >40 mg/L (>381 mnol/L) and ferritin level >500 ng/mL (>1,123 pmol/L)	
Rheumatologic disease?	Concern for MAS/HLH, consider treatment with corticosteroids, IVIg, anakinra (54)
Cancer?	Concern for MAS/HLH, consult specialist
Infection/sepsis?	Consider uncontrolled inflammatory response spectrum: MAS/MALS/HLH Refer to specialist, mortality risk (CRP level >40.8 mg/L [>389 nmol/L], ferritin level >1,980 ng/mL [>4,449 pmol/L]) (45)
Familial HLH?	Refer to specialist (ferritin level >10,000 ng/mL [>22,470 pmol/L])

CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, GvHD=graft-versus-host disease, HLH=hemophagocytic lymphohistiocytosis; IVIg=intravenous immunoglobulin, MALS=macrophage activation–like syndrome, MAS=macrophage activation syndrome, sJIA=systemic juvenile idiopathic arthritis, SLE= systemic lupus erythematosus.

pathway, promoting phagocytosis. (59) Although deficient in liver failure, (5) it can be elevated in several differing inflammatory states. Furthermore, CRP remains accurate in protein wasting conditions such as nephrotic syndrome. (60) Elevated CRP level is generally associated with significant infection or tissue injury (Table 1).

Infections

Clinically, an increase in CRP level indicates that the body is mounting an appropriate inflammatory response to bacterial by-products, a response that promotes macrophage phagocytosis. It rapidly rises with acute inflammation and similarly clears quickly with resolution of inflammation. One of the most widely used applications of CRP is in the diagnosis of bacterial infection. One study in adult ICU patients demonstrated that increases in CRP levels greater than 87 mg/L (>829 nmol/L) actually were more specific for proven bacterial or fungal infection than was elevated temperature and that the combination of an elevated CRP level and fever increased specificity for bacterial ventilator-associated pneumonia, as defined by persistent radiographic findings, high or low white blood cell count, fever, and purulent secretions, to 100% in the 50 patients with pneumonia captured in this study. (6) A recent systematic literature review demonstrated the efficacy of CRP level in ruling in or out serious bacterial infection with fever at first presentation. (7) This review's pooled estimate of specificity and sensitivity were 0.79 and 0.77, respectively, with variable CRP levels (20–70 mg/L [190–667 nmol/L]). The studies demonstrated reasonable specificity (75%–96%) in all cases. Furthermore, the studies had good sensitivity in serious bacterial infection (62%–89%), with less sensitivity (22%–58%) in studies that included all bacterial infections as opposed to only serious cases. (8)(61)(62)(63)(64)(65)(66)(67)(68) These studies are summarized in Table 3.

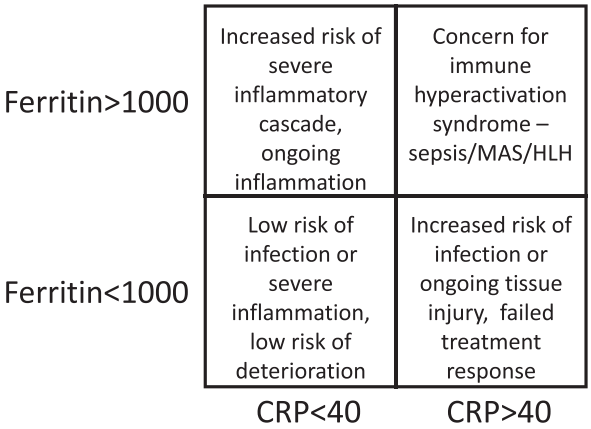

Figure. The use of ferritin (μg/L) and C-reactive protein (CRP) (mg/L) levels to differentiate ongoing inflammatory cascade, risk of infection or tissue injury, or immune hyperactivation and concern for sepsis/macrophage activation syndrome/hemophagocytic lymphohistiocytosis spectrum syndromes.

More recent studies have examined combinations of biomarkers with CRP to increase its predictive value. The combination of CRP level (>100 mg/L [>952 nmol/L]) and procalcitonin level (>2 ng/mL [>2 μg/L]) has been shown to accurately assist in the prediction of serious bacterial infection in febrile infants without a source of infection, although procalcitonin testing is not yet widely available. (8)

Similarly, when applied to select populations, CRP level can assist in the differentiation of bacterial and nonbacterial infections. A study of infants requiring ICU admission demonstrated that CRP level was significantly elevated in

TABLE 3. **CRP Specificity and Sensitivity with Given CRP Cutoff Levels for Bacterial Infection**

SOURCE	CRP LEVEL, mg/L (nmol/L)	SENSITIVITY, %	SPECIFICITY, %	
Serious bacterial infection				
Isaacman and Burke, 2002 (61)	44 (419)	62	81	LR+3.3 LR-0,47
Pulliam et al, 2001 (62)	70 (667)	79	90	LR+7.9 LR-0,23
Lacour et al, 2001 (63)	40 (381)	89	75	LR+3.6 LR-0,15
Galetto-Lacour et al, 2003 (8)	40 (381)	79	79	LR+3.8 LR-0,27
Berger et al, 1996 (64)	20 (190)	83	67	LR+2.5 LR-0,25
Andreola et al, 2007 (65)	40 (381)	71	81	LR+3.7 LR-0,36
Bacterial infection				
McCarthy et al, 1978 (66)	60 (571)	44	86	LR+3.1 LR-0,65
Tejani et al, 1995 (67)	20 (190)	22	94	LR+3.7 LR-0,83
Cobben et al, 1990 (68)	35 (333)	58	96	LR+14.5 LR-0,44

CRP=C-reactive protein.

patients with bacterial infections, with more specificity than white blood cell count if the CRP level was greater than 50 mg/L (>476 nmol/L). (10) This is supported in well-appearing infants with fever without a source, with significant elevation of CRP levels (>200 mg/L [>1,905 nmol/L]), especially after 12 hours of fever. (11) CRP level combined with interleukin (IL)-6 level can also aid in the differentiation of fungal versus bacterial late-onset neonatal sepsis, (12) although IL-6 assays are costly and have limited availability.

The value of the CRP biomarker has been examined in the setting of immune suppression as well. In pediatric patients with febrile neutropenia, CRP level was significantly elevated in children with culture-positive infections compared with those with culture-negative infection or fever of unknown source. (68) Furthermore, CRP level showed significant increases in patients who failed first-line antibiotic drug therapy and required second-line antibiotic drugs or, after this, antifungal drug coverage. (16) Similar results showed elevation of CRP level combined with procalcitonin level, indicating incorrect treatment and response with appropriate treatment. (16) Furthermore, in neutropenic children with persistent fever at 4 days, an elevated CRP level (>90 mg/L [>857 nmol/L]) and absolute monocyte count (<100/μL) suggested invasive fungal disease. (13) The use of CRP level in predicting bacterial infection is further supported through a recent meta-analysis of febrile neutropenia, which found that in more than 25 studies examining 14 different biomarkers, the only biomarker that consistently demonstrated value beyond clinical decision rules was the CRP level as an indication of infection. (69)

The relation between CRP level and bacterial infection has also been shown in pediatric osteomyelitis and septic arthritis. A normal CRP level (<20 mg/L [<190 nmol/L]) and ESR effectively rule out most cases of acute bacterial bone and joint infection, (17) although some small bone osteomyelitis may present initially with a negative CRP. Furthermore, normalization of CRP level (<30 mg/L [<286 nmol/L]) during intravenous antibiotic drug treatment of osteomyelitis or septic arthritis indicates the appropriate time for transition to oral antibiotic drug therapy. (18)

Surgery

Beyond the appropriate elevation of CRP level as an inflammatory response to an infectious process, there are other clinical circumstances that can cause elevation of CRP level. CRP elevation has been noted in postsurgical patients, although there is significant evidence that the level and duration of CRP elevation can still be used for detection of infection. A cohort of neonates without infection had a significant elevation in CRP level on the first and second postoperative days, with normalization by day 3; without CRP level normalization, postoperative complication, primarily bloodstream infection or bowel perforation, was more likely. (19) A recent study of pediatric patients undergoing congenital heart surgery demonstrated that increases in CRP level greater than 40 mg/L (>381 nmol/L) per day

had a positive predictive value of 86% and specificity of 95% for bacterial infection compared with febrile patients without infection. (20) Another prospective observational study including all pediatric surgical postoperative patients with a CRP level greater than 110 mg/L (>1,048 nmol/L) on postoperative day 3 demonstrated sensitivity of 87% and specificity of 89% for bacterial infection. (21) CRP can also rule out peritonitis after acute appendicitis (CRP level <30 mg/L [<286 nmol/L]) with sensitivity of 95% and a negative predictive value of 96%, although CRP level cannot be used to make the diagnosis of peritonitis (specificity=74%, positive predictive value=68%). (22)

Transplant

After transplant, CRP level can be elevated for a variety of reasons, leading to variable usefulness. In postoperative pediatric kidney transplant patients, CRP level normalization within 5 to 10 days is associated with favorable outcomes. Normalization was not seen in patients with complications such as acute rejection, infection, or thrombosis. The most significant elevations were noted in bacterial infection (88% of patients), but in this population, CRP level was also elevated in viral infections (73%), acute rejection (68%), and thrombosis (82%). The study did find CRP response to rejection therapy in 86% of patients and found that CRP level greater than 20 mg/L (>190 nmol/L) was more sensitive than fever or white blood cell count in prediction of all complications. (23) Similarly, CRP level elevation in pediatric bone marrow transplant patients correlates with bacterial or fungal infections and with severe acute graft-versus-host disease (CRP level >43.5 mg/L [>414 nmol/L]). CRP level elevation also correlates well with nonrelapse mortality (CRP level >70.5 mg/L [>671 nmol/L]). (24) Importantly, CRP level is inaccurate in acute liver or liver transplant failure because production in the liver is interrupted.

Inflammatory Bowel Disease

Inflammatory bowel disease, including Crohn's disease and ulcerative colitis, is associated with elevated CRP levels. Shine et al (25) showed that CRP level can successfully differentiate between children with inflammatory bowel disease and children with functional abdominal pain. CRP level does correlate with disease state, and this has been validated with cutoff values as low as 5 mg/L (48 nmol/L) for inflammatory bowel disease, and some groups encourage routine screening of children with chronic abdominal symptoms. (26)(70)

Autoimmune Disease

One of the most intriguing areas of interest in CRP is this protein's role in autoimmunity and rheumatic disease. CRP level is not normally elevated in the most common subtypes of juvenile idiopathic arthritis, oligoarticular and polyarticular; however, when it is elevated it correlates with highly active disease and poor prognosis regarding response to initial therapy and ability to obtain remission. (27) If CRP level is elevated, it is useful to monitor response to therapy and is included in the American College of Rheumatology pediatric measures of improvement criteria. (28) CRP level and ESR are also included in the Juvenile Arthritis Disease Activity Score, a validated scale, although that same validation study demonstrated that CRP as a stand-alone laboratory test correlates closely to clinical activity scoring. (29) High CRP level (>50 mg/L [>476 nmol/L]) at the time of diagnosis has correlated with poor therapeutic response and failure of first remission, and elevated levels after 6 months of treatment also indicate a poor prognosis. (27) When CRP level is markedly elevated in the context of newly diagnosed arthritis, systemic juvenile idiopathic arthritis (sJIA) must be considered. These patients are most at risk for developing macrophage activation syndrome (MAS). Interestingly, in these patients CRP level will remain elevated and ESR will paradoxically drop to normal levels. (49)

CRP level is also included in the diagnostic criteria for Kawasaki disease. (30) A normal CRP level has an excellent negative predictive value for Kawasaki disease, whereas a CRP level greater than 100 mg/L (>952 nmol/L) is an indicator for this vasculitis. (31) Subsequent work has demonstrated heterogeneity of disease with variable elevation of CRP level, with greater elevation associating with coronary artery lesions. (32)(71) In a retrospective review, patients with CRP levels greater than 80 mg/L (>762 nmol/L) after initial treatment with intravenous immunoglobulin (IVIg) are more likely to require additional IVIg treatment or other secondary therapy beyond IVIg. ESR uncouples from inflammation after treatment, making CRP the test of choice for response. (33)

Work in other pediatric rheumatologic disease is limited. Unlike in vasculitis (Kawasaki disease and sJIA, for example), CRP level does not rise substantially in active systemic lupus erythematosus or juvenile dermatomyositis. The most useful employment of CRP level in these disease types is for differentiation of disease flare from infection, especially in the setting of chronic immunosuppression. (34)(35)

Severe Illness

One of the most striking studies of CRP demonstrated in an ICU population that high CRP levels (>100 mg/L [>952

nmol/L]) are associated with organ failure and death, and persistently high levels are associated with poor outcomes, indicating requirements for more aggressive interventions, including hemodynamic, respiratory, or renal support, to prevent morbidity and mortality. (36)

Hemophagocytic lymphohistiocytosis (HLH) and MAS have also been associated with significant elevations in CRP level, and patients with viral disease, rheumatologic disease, and malignancy compose a significant proportion of patients with these syndromes. (72) These patients also have significant elevations in ferritin levels and are discussed later herein.

FERRITIN ELEVATION

Ferritin is a protein involved in iron storage and has been used clinically as a marker of total body iron stores. The test is widely available and commonly ordered when evaluating for iron deficiency in infants and children. In the body, ferritin binds iron, protecting lipids, DNA, and proteins from potential free radicals that can be formed by free iron. Ferritin is also an acute-phase reactant that is elevated in many conditions aside from anemia, (73) and although traditionally hypoferritinemia is used as a measure of iron deficiency or malnutrition, elevation in this biomarker has recently been recognized as a marker of several disease states (Table 1). A recent review of all patients with elevated ferritin levels (>500 ng/mL [>1,123 pmol/L]) in a pediatric referral center demonstrated elevated levels in a variety of disease processes, with most being found in patients with transfusion dependence, infection (viral and bacterial), autoimmunity, stem cell transplant, malignancy, and renal disease. This study also showed that the highest levels of ferritin were found in HLH (range, 994–189,721 ng/mL [2,233–426,303 pmol/L]). (74) Elevated ferritin and CRP levels represent an ongoing inflammatory process in the majority of ill patients (Fig). (45)

Iron Overload

Hyperferritinemia is most commonly seen in patients with significant iron overload. The classic iron overload disease is hereditary hemochromatosis, an inherited dysregulation of the iron transport system that can lead to total body iron overload. This disease can lead to hepatic cirrhosis and hepatocellular carcinoma. Recent work has demonstrated that hyperferritinemia (ferritin level >1,000 ng/mL [>2,247 pmol/L]) is a hallmark of iron overload disease in hereditary hemochromatosis. (37)(38)(39)(40) In neonates with acute liver failure, neonatal hemochromatosis must be considered, and these patients show similar marked elevation in ferritin levels. (41) Neonatal hemochromatosis also has been suggested to be a form of autoimmune hepatitis caused by gestational alloimmunization by maternal antibodies against the neonatal liver. (75)

Ferritin has long been known to be an indicator of iron stores, and it functions well to differentiate anemic states. Chronic hemolytic anemias such as sickle cell disease and β-thalassemia have significant elevations in ferritin levels, which differentiates them from iron deficiency anemia. (42) Elevated ferritin levels are also seen in other congenital hemolytic anemias, such as congenital dyserythropoietic anemia and congenital sideroblastic anemia. (43) Most recently, ferritin's role in monitoring iron overload has been supplanted by more accurate magnetic resonance imaging studies. (76)

Infection

The exact source of serum ferritin is unknown, but suspected sources include the liver, kidney, and macrophages. Recent work by Cohen et al (77) demonstrated that in mice, macrophages are the primary source of serum ferritin. This may explain the association between elevated ferritin levels and infection. The ferritin level has been shown to be significantly elevated in episodes of infection and has been hypothesized to sequester iron from infectious agents that may use iron as a nutrient source. Kossiva et al (78) demonstrated significant ferritin level elevation in pediatric patients with fever. Another recent study demonstrated significant elevation of ferritin levels in acute Epstein-Barr virus infection. This was in contrast to CRP level, which remained normal. (44) Another study looking at children with severe sepsis and septic shock found that ferritin level was significantly elevated in most patients and demonstrated that levels of ferritin greater than 500 ng/mL (>1,123 pmol/L) correlated with mortality. (46) Similar work by Bennett et al found that among all pediatric patients with ferritin tests in an academic center, those with significantly elevated levels (>3,000 ng/mL [>6,741 pmol/L]) had significantly higher risks of ICU admission and mortality. (48) Another recent study performed in a large cohort of adult ICU and emergency department patients with suspected infection and meeting 2 systemic inflammatory response syndrome (SIRS) criteria demonstrated significantly worse morbidity and mortality in patients with ferritin levels greater than 4,420 ng/mL (>9,932 pmol/L) and an association with a hyperinflammatory syndrome with elevated proinflammatory cytokine levels. The authors of that study termed this state *macrophage activation–like syndrome* because of its similarities with MAS. (47)

Autoimmune Disease

Bennett et al (48) also noted that the highest levels of ferritin were seen in patients with rheumatologic disease and bone marrow transplants. Adult-onset Still disease commonly presents with hyperferritinemia, but, as the name suggests, this is an adult disease. (79) The pediatric-onset equivalent, sJIA, typically demonstrates elevated ferritin levels at diagnosis and shows response to treatment with glucocorticoids. (80) Importantly, the prevalence of MAS in sJIA is 7% to 13%, and an elevated ferritin level (>500 ng/mL [>1,123 pmol/L]) in these patients should prompt investigation for this syndrome. (49) Another recent study demonstrated usefulness in the use of ferritin levels to differentiate sJIA (without MAS) from Kawasaki disease. This same study demonstrated in patients with Kawasaki disease that those with significant ferritin level elevation developed refractory disease and tended to require repeated IVIg treatment or plasma exchange therapy. Only a single patient with Kawasaki disease in this study developed MAS, and no patients with sJIA met the MAS criteria, but IL-18 levels were suggested to be useful in assisting in the differentiation of Kawasaki disease with MAS from sJIA. (81) A study of biomarkers in juvenile dermatomyositis demonstrated that elevated ferritin levels associated with rapidly progressive interstitial lung disease, a major cause of death in this population, and an elevated ferritin level may indicate a need for early aggressive treatment. (82) There is limited information on ferritin levels in pediatric systemic lupus erythematosus, although the occurrence of fever and cytopenia with hyperferritinemia (ferritin level >500 ng/mL [>1,123 pmol/L]) should raise concern for MAS in this disease. (50)

Bone Marrow Transplant

Ferritin level has been shown to have clinical usefulness in patients undergoing bone marrow transplant for hematologic malignancy. Adult studies have shown that lower survival rates correlate with elevated pretransplant ferritin levels, and this work has been supported in pediatric patients showing elevated ferritin levels (>110 ng/mL [>247 pmol/L]) associated with hepatic, endocrine, and cardiac dysfunction. (51) A similar pediatric study determined that ferritin levels greater than 1,000 ng/mL (>2,247 pmol/L) correlate with increased treatment-related mortality. This same study demonstrated that iron chelation therapy decreased mortality rates to the same rate as patients with lower ferritin levels. (52) Elevated ferritin levels also indicate an increased risk of hepatic veno-occlusive disease after stem cell transplant in the pediatric population. (53) Studies have shown that adults with elevated pretransplant ferritin levels have significant increases in risk of bloodstream infections, septic shock, and sepsis with organ failure, although this has not been examined in children. (83)(84) Another recent study demonstrated that graft rejection in allogeneic hematopoietic stem cell transplant was preceded by a 77-fold increase in ferritin 1 to 7 days before the onset of symptoms. (85)

COMBINED FERRITIN AND CRP ELEVATION

Finding a combination of substantial elevation of CRP and ferritin levels warrants consideration of HLH and MAS. A recent review of MAS in pediatric rheumatologic patients demonstrated significant elevation of ferritin and CRP levels in 88% and 85% of patients, respectively. (54) These are 2 easily testable markers that can be checked quickly if this diagnosis is suspected clinically. The most recent diagnostic criteria for HLH requires 5 of 8 characteristics: 1) fever, 2) cytopenia of 2 cell lines, 3) hypertriglyceridemia or hypofibrinogenemia, 4) hyperferritinemia (ferritin level >500 ng/mL [>1,123 pmol/L]), 5) hemophagocytosis, 6) elevation in soluble IL-2 receptor level, 7) decreased natural killer cell activity, and 8) splenomegaly. (86) Unfortunately, as these diagnostic criteria have been applied to clinical practice, it has been recognized that there is overlap between these criteria and a broad range of uncontrolled inflammation syndromes, including sepsis, SIRS, multiple organ dysfunction syndrome (MODS), MAS, and secondary and primary HLH. The recognition of this overlap has brought to light that these clinical syndromes represent a spectrum of uncontrolled inflammation that has become harmful to the body. (87) There are few other clinical scenarios in which CRP and ferritin levels are simultaneously elevated, and these scenarios primarily fall on the sepsis/SIRS/MODS/MAS/HLH spectrum, as demonstrated in bone marrow transplant patients. (84) A recent prospective cohort study examining pediatric patients with severe sepsis demonstrated that the combined elevation of CRP level (>40.8 mg/L [>389 nmol/L]) and ferritin level (>1,980 ng/mL [>4,449 pmol/L]) is associated with a high risk of mortality. (45) The combined elevation of CRP and ferritin levels should raise concern for severe immune hyperactivation on the sepsis/MAS/HLH spectrum. Furthermore, this same study observed that if these 2 markers normalized, the risk of mortality was significantly reduced, whereas if they remained elevated, mortality remained high. There has been limited research into how disease outcomes are affected by the knowledge gained from these clinical markers beyond the effects on treatment discussed

previously, but CRP and ferritin levels should assist in early diagnosis and treatment, which should affect outcomes. Further work in this area in severely ill patients is warranted to determine whether these markers can improve outcomes in the future.

CLINICAL DECISION PATHWAY FOR ELEVATED CRP AND FERRITIN LEVELS

Considering the diverse literature available on elevated CRP and ferritin levels in pediatric practice and the availability of the tests in standard clinical laboratories, CRP and ferritin levels can be easily and readily integrated into daily clinical practice for pediatricians. Furthermore, frequently physicians obtain these tests and are at a loss as to how to use the results. To this end, various pediatric specialists contributed to the design of a systematic summary of evidence for the investigation and clinical decision making surrounding elevated CRP and ferritin levels. Per the clinical experience of this multidisciplinary group and based on available scientific evidence, we composed Tables 1 and 2 for general pediatricians and pediatric trainees for decision-making guidance in the setting of elevated inflammatory markers. Importantly, the biomarkers cannot supplant clinical decision making, and evidence presented in this review should be used only as an adjunct to clinical practice. Furthermore, this evidence is based specifically on the review of literature and the consensus of the authors after review of the literature. CRP and ferritin levels cannot be used in isolation and must be considered only in appropriate clinical situations to assist in guidance of therapy, not as a driver of therapy.

CONCLUSIONS

CRP and ferritin levels, commonly available biomarkers, have wide and varying uses in the clinical world of pediatrics. We outlined the evidence currently available and through the contribution of pediatric specialists derived a clinical systematic summary of evidence to determine the etiology of fever for pediatric patients by incorporating CRP and ferritin levels. CRP level elevation in the setting of fever could indicate infection, especially in patients with renal disease, or disease flare in inflammatory bowel disease or pancreatitis. It can also be followed for response to treatment in graft-versus-host disease. Ferritin level elevation can indicate sJIA, HLH, MAS, malignancy, or iron overload. Viral infection, especially in the posttransplant setting, must also be considered. Furthermore, the combination of elevations in CRP and ferritin levels can indicate a severe inflammatory process and impending morbidity. These markers in combination can guide treatment in sepsis/SIRS/MODS/MAS/HLH and are particularly helpful when monitored for signs of response. Unfortunately, much of the evidence available remains variable, and CRP and ferritin levels remain nonspecific without clinical correlation and other supporting laboratory findings. CRP and ferritin levels cannot be used in isolation and should not be obtained without a clinical question that will be influenced by a normal or elevated laboratory result. These serological markers of inflammation are widely available and easily monitored, which are desirable characteristics for clinical decision making in pediatric fever and warrant further investigation for clinical decision-making models, especially in relation to the uncontrolled inflammatory response.

Summary

- Based on research evidence, C-reactive protein (CRP) and ferritin levels can be used to indicate uncontrolled inflammation in pediatric practice and should be considered in making treatment decisions based on the clinical context. In the setting of fever without a clear source, CRP and ferritin levels can assist in guiding diagnostic and treatment decisions.
- Based on research evidence and clinical consensus, CRP level greater than 40 mg/L (>381 nmol/L) and ferritin level greater than 1,000 ng/mL (>2,247 pmol/L) should be considered highly concerning for severe infection with uncontrolled inflammation and indicate significantly increased mortality risk (Fig). These values should be considered early warning signs of severe impending illness.

References for this article are at http://pedsinreview.aappublications.org/content/41/4/172.

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1. As a pediatric hospitalist you are taking care of a 2-week-old boy who has been having persistent high fevers. All cultures, including blood, urine, and cerebrospinal fluid, are negative. Preliminary viral testing for influenza and respiratory syncytial virus is negative. Extended viral testing is pending. You are trying to decide whether you can stop administering antibiotic agents. You order a C-reactive protein (CRP) test, which showed a level of 250 mg/L (2,381nmol/L). Assuming that your hospital laboratory has procalcitonin readily available, which of the following procalcitonin levels, in combination with the CRP, is highly predictive of the presence of serious bacterial infection in this febrile infant?
   A. 0.1 ng/mL (0.1 μg/L).
   B. 0.5 ng/mL (0.5 μg/L).
   C. 1.0 ng/mL (1.0 μg/L).
   D. 1.5 ng/mL (1.5 μg/L).
   E. 2.5 ng/mL (2.5 μg/L).
2. You are caring for a 3-month-old girl on the inpatient team with fever for 30 days without an obvious source. She was initially diagnosed as having a urinary tract infection and completed a 10-day course of cefdinir, and repeated urine cultures are negative. She has a CRP level of 100 mg/L (952 nmol/L), and her absolute monocyte count is 50. Anaerobic and aerobic blood cultures are pending, and the child is taking vancomycin and cefepime. Which of the following is the most appropriate next step in the management of this patient?
   A. Adjust antibiotic drug choice to broaden the spectrum of antibiotic coverage.
   B. Continue the current antibiotic drug regimen and obtain peak and trough drug levels.
   C. Discontinue all antibiotic agents because the fever could be a drug fever.
   D. High-volume blood culture for bacteria to be performed with temperature spikes.
   E. Obtain fungal cultures and start antifungal drug therapy empirically.
3. An 8-year-old girl began having daily fevers up to 102°F to 103°F (38.9°C–39.4°C) starting on postoperative day 3 after an appendectomy. The patient also has some upper respiratory tract infection symptoms. A CRP test was ordered by the surgical team and showed a level of 200 mg/L (1,905 nmol/L). Which of the following is the most likely possible cause of increased CRP level and fevers in this patient that should be investigated further?
   A. Drug fever due to the anesthetics.
   B. Fungal infection.
   C. Postsurgical stress.
   D. Serious bacterial infection.
   E. Upper respiratory tract infection.
4. An 8-year-old boy was diagnosed as having polyarticular juvenile idiopathic arthritis 6 months ago. He has been on treatment with disease-modifying agents and is followed in the pediatric rheumatology clinic. He returned today for follow-up. His initial CRP level at the time of diagnosis was 50 mg/L (476 nmol/L). His CRP level today continues to be elevated at 70 mg/L (667 nmol/L), and his ferritin level is 1,100 ng/mL (2,471 pmol/L). The parents are concerned and ask your opinion about the laboratory results. Which of the following is the most accurate explanation of the laboratory findings in this patient?
   A. Reassure the family because the CRP level is not expected to normalize until the patient is on treatment for more than 12 months.
   B. The diagnosis is most likely incorrect and further testing must be performed.
   C. The patient is most likely resistant to the treatment regimen.
   D. The patient's disease will most likely have a poor prognosis.
   E. The presence of concomitant infection must be ruled out.

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5. You are treating a 5-year-old boy with Kawasaki disease who continues to run a fever (temperature >103°F [>39.4°C]) after intravenous immunoglobulin treatment 36 hours earlier. His ferritin level has been persistently elevated (>1,000 ng/mL [>2,247 pmol/L]). His initial echocardiographic findings were negative. Which of the following is the most appropriate next step in therapy that will affect the outcome in this patient?

   A. Repeat echocardiography in 1 week.
   B. Repeat intravenous immunoglobulin treatment.
   C. Start acetaminophen therapy around the clock to treat the fever.
   D. Start intravenous corticosteroid therapy.
   E. Watchful waiting and reassurance.

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