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A Clinical Prediction Algorithm to Stratify Pediatric Musculoskeletal Infection by Severity

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Abstract

Objective—There are currently no algorithms for early stratification of pediatric musculoskeletal infection (MSKI) severity that are applicable to all types of tissue involvement. In this study, the authors sought to develop a clinical prediction algorithm that accurately stratifies infection severity based on clinical and laboratory data at presentation to the emergency department.

Methods—An IRB-approved retrospective review was conducted to identify patients aged 0–18 who presented to the pediatric emergency department at a tertiary care children's hospital with concern for acute MSKI over a five-year period (2008–2013). Qualifying records were reviewed to obtain clinical and laboratory data and to classify in-hospital outcomes using a three-tiered severity stratification system. Ordinal regression was used to estimate risk for each outcome. Candidate predictors included age, temperature, respiratory rate, heart rate, C-reactive protein, and peripheral white blood cell count. We fit fully specified (all predictors) and reduced models (retaining predictors with a p-value < 0.2). Discriminatory power of the models was assessed using the concordance (c)-index.

Results—Of the 273 identified children, 191 (70%) met inclusion criteria. Median age was 5.8 years. Outcomes included 47 (25%) children with inflammation only, 41 (21%) with local infection, and 103 (54%) with disseminated infection. Both the full and reduced models accurately demonstrated excellent performance (full model c-index 0.83, 95% CI [0.79–0.88]; reduced model

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0.83, 95% CI [0.78–0.87]). Model fit was also similar, indicating preference for the reduced model. Variables in this model included C-reactive protein, pulse, temperature, and an interaction term for pulse and temperature. The odds of a more severe outcome increased by 30% for every 10-unit increase in C-reactive protein.

Conclusions—Clinical and laboratory data obtained in the emergency department may be used to accurately differentiate pediatric MSKI severity. The predictive algorithm in this study stratifies pediatric MSKI severity at presentation irrespective of tissue involvement and anatomic diagnosis. Prospective studies are needed to validate model performance and clinical utility.

Introduction

Pediatric musculoskeletal infections (MSKI) represent a diagnostic and management challenge due to overlap in clinical presentation with common non-infectious conditions (eg, toxic synovitis). Further complicating care of these children is the ineffectiveness of algorithms at rapidly determining the anatomic location (muscle, bone and/or joint) and severity of infection^{1,2}. In those with serious infection, uncertainty may lead to delays in diagnosis and intervention with antibiotics and debridement. Conversely, those without infection may suffer from unneeded treatments or even hospitalization.

Prior studies by Kocher et al. and Caird et al. proposed algorithms for differentiating between septic arthritis of the hip and toxic synovitis based on clinical and laboratory data^{3,4}. While these predictive algorithms vastly improve clinicians' ability to triage patients, they are limited in scope to the hip joint. Similarly, Copley et al. developed a severity scoring system for acute hematogenous osteomyelitis in children that correlated well with in-hospital outcomes⁵. However, this scoring system uses data obtained during hospitalization, not in the emergency department, and is only applicable to those with known osteomyelitis. No prediction algorithms exist that stratify the severity of pediatric MSKI of bone, muscle and/or joint at presentation in the emergency department.

In this study, we sought to develop a clinical prediction algorithm which accurately differentiates non-infectious illness, local infection, and disseminated infection based on clinical and laboratory data at presentation in children with concern for MSKI. We tested the hypothesis that patients' illness severity may accurately be predicted based on clinical and laboratory data obtained in the emergency department.

Methods

An IRB-approved retrospective review of the pediatric orthopedic consult list was conducted to identify children 0–18 years of age who presented to the pediatric emergency department at a tertiary care children's hospital with concern for acute MSKI over a five-year period (2008–2013). Patients with post-traumatic or post-operative infection, post-streptococcal reactive arthritis, acute rheumatic fever, chronic infection (eg, fungal or mycobacterial infection, chronic recurrent multifocal osteomyelitis), necrotizing fasciitis, and cellulitis were excluded.

Qualifying records were reviewed and children were identified as having inflammation only, local infection, or disseminated infection using the operational definitions provided in Table 1 from Mignemi et al.⁶ These definitions were validated through statistical comparisons of in-hospital outcomes between each group (data not shown). Demographics (eg, age), vital sign parameters, and laboratory data obtained in the emergency department were collected from the electronic medical record.

Ordinal logistic regression was used to estimate risk (expressed as percentages) for MSKI (inflammation, localized infection, or disseminated infection). This modeling strategy estimates a single beta coefficient for each predictor and is analogous to a summary of the odds ratios obtained from separate binary logistic regression models^{7–9}. It also allows for the estimation of risk for each outcome (eg, disseminated infection) as well as risk for more than one outcome (eg, local or disseminated infection) using a single model.

Variables included in the ordinal logistic regression were selected *a priori* and based on clinical judgment or inclusion in prior studies^{4,5,10}. Candidate predictors included age, temperature, respiratory rate, heart rate, C-reactive protein, and peripheral white blood cell count. Laboratory values were limited to those collected at the time of presentation. All predictors were maintained as continuous variables. We first fit a fully specified model that included all candidate predictors, plus interaction terms between age and heart and respiratory rates as well as heart rate and temperature. Next, we derived a reduced model that retained only those variables from the fully specified model with a p-value of 0.2 or less. A likelihood-ratio test was used to compare goodness of fit between the two models. Akaike Information Criterion (AIC) values, which assess model fit (with penalization for model complexity) were also calculated⁷.

Predictive performance of the prognostic models was estimated by measuring each model's discriminatory power using the concordance (c)-index, which assesses a model's ability to differentiate between children with and without each outcome. A c-index of 1.0 indicates perfect concordance between observed and predicted outcomes, whereas a c-index of 0.5 is analogous to a coin flip. All analyses were conducted using Stata 14 (StataCorp, College Station, TX).

Results

We identified 273 children during the study period. After exclusions, 202 (74%) records were reviewed. Of these, 191 (95%) children with complete outcome and predictor data were included in this study; 47 (25%) children had a non-infectious process, 41 (21%) had localized disease, and 103 (54%) had disseminated disease. Patient characteristics are reported in Table 2 and hospital outcomes are reported in Table 3. There were no significant differences between the groups with respect to age, gender, ability to bear weight at presentation, or history of trauma immediately before presentation. However, children with more severe disease had significantly longer hospital length of stay, were more likely to go to the intensive care unit, and had a longer duration of antibiotics. There were also significant differences between groups in vital signs and laboratory markers measured in the emergency department.

Both the fully specified model and the reduced model accurately discriminated among the three outcome levels (full model c-index 0.83, 95% CI [0.79–0.88]; reduced model 0.83, 95% CI [0.78–0.87]). Model fit was also similar (likelihood ratio test $p=0.67$; full model AIC 315; reduced model 308), indicating preference for the more parsimonious reduced model. The variables included in this model were CRP, pulse, temperature, and an interaction term for pulse and temperature. The results of the multivariate analysis for this model are displayed in Table 4. Adjusted odds ratios and 95% confidence intervals for CRP (10-unit increase) and pulse (10-unit increase at four specified temperature values) are reported.

The association between presentation CRP and predicted risk for local or disseminated infection and disseminated infection alone estimated from the reduced model (holding all other variables constant at their median values) is presented in Figure 1 and Table 5.

Discussion

This study demonstrates that clinical and laboratory data obtained in the emergency department may be used to accurately stratify pediatric musculoskeletal disease severity into inflammatory, localized, and disseminated classifications. The variables included in the reduced predictive model were presentation CRP, pulse, temperature, and an interaction term between temperature and pulse. This model represents a novel clinical prediction algorithm for pediatric MSKI that is applicable to all types of tissue involvement.

The inclusive approach to musculoskeletal infection was selected because it is often difficult to distinguish between superficial or deep infections and infections involving one or multiple tissue types at presentation. Including all types of musculoskeletal infection in the prognostic model reflects clinical practice.¹¹

Inflammatory markers, respiratory rate, white blood cell count, and temperature are commonly used indicators to gauge infection severity^{12,13}. Kocher et al. and others have developed criteria for identifying septic arthritis and stratifying osteomyelitis severity that include CRP, ESR, temperature, weight-bearing status, respiratory rate, and white blood cell count at presentation^{3–5}. However, we were surprised to find that white blood cell count and respiratory rate did not have a statistically significant contribution to our severity stratification model. Although elevation in these markers may be indicative of an inflammatory or infectious process, this result suggests that they are not sufficient to stratify infection severity at presentation. On the other hand, presentation CRP was the strongest predictive indicator of MSKI severity in the model. This finding is consistent with severity prediction models for a range of different pathologies where CRP, but not white blood cell count, correlated with disease severity^{14–17}.

The algorithm that we developed can guide treatment and diagnosis of pediatric MSKI by helping physicians identify patients at higher risk of complications. Patients with disseminated infection are at higher risk for systemic diseases such as sepsis, thromboembolism, and coagulopathy^{18–21}. Identifying and treating these potential

complications earlier could improve outcomes. Similarly, rapidly identifying patients who have a low risk for infection would enable less intensive treatment and earlier discharge.

The predictive model generated in this study has several limitations. First, the model was developed using data collected from patients at a single tertiary care children's hospital with a high probability of having musculoskeletal infection that required an orthopaedic surgery consult. Therefore, the authors expect that the models are most applicable at an institution with a similar patient population with relatively few patients with non-serious infection. It will be important to validate the model in a future prospective study that includes an expanded population of children. In addition, conditions such as autoimmune, neoplastic, and viral diseases may present similarly to musculoskeletal infection, but were not included in this study. Predictive models developed in future studies may be improved by including such conditions in the analysis. Furthermore, models that include one disease process such as septic arthritis may indeed be more accurate than the model described here once the diagnosis is known and future comparisons between models would be helpful. However, this model was developed to be applicable at presentation prior to a known diagnosis and provide increased impetus for early advanced imaging and treatment in a child with a high risk of severe infection.

Overall, this study demonstrates that patients with suspected MSKI may be stratified based on infection severity soon after presentation to the emergency department. The predictive model generated in this study has the potential to improve triage of patients and direct hospital resources towards patients with more severe and disseminated disease. Prospective studies are needed to validate the effectiveness of these predictive models.

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Figure 1. Predicted Risk of Infection and Disseminated Infection Stratified by CRP at Presentation

The predicted risks of having infection (local or disseminated) or disseminated infection are represented graphically with percent probability on the y-axis and presentation CRP on the x-axis. Probabilities estimated from reduced model, holding all other variables constant at their median values. Error bars represent 95% confidence interval.

Table 1

Operational Definitions of Infection Severity

	Definition
Inflammation	<i>All of the following (if available) must be true:</i> No imaging diagnostic for infection Negative local culture (when available) Negative blood culture Fluid/tissue without evidence of infection
Local Infection	<i>At least one of the following must be true:</i> Imaging diagnostic for infection in one anatomic site Local culture positive AND/OR fluid/tissue consistent with infection * One positive blood culture
Disseminated Infection	<i>At least one of the following must be true:</i> Imaging diagnostic for infection in multiple anatomic sites AND/OR multiple compartments Two or more positive blood cultures Two or more positive tissue cultures from multiple anatomic sites Thromboembolic disease

* grossly purulent, cell count >50,000

Table 2

Patient Admission Data

	Inflammation (n=47)	Local Infection (n=41)	Disseminated Infection (n=103)	p-value*
Age (years)	4.95 (3.35–6.63)	4.99 (1.93–10.45)	6.21 (2.98–9.93)	0.21
Gender (% M)	68	68	59	0.22
Non-weight bearing at presentation (%)	61.7	61.0	68.9	0.35
History of trauma (%)	19.1	17.1	24.3	0.29
CRP (mg/L)	4.3 (1.3–17.8)	32.7 (16.6–84.2)	80.0 (40.5–160.7)	<0.001
WBC (cells/ul)	11.2 (8.6–13.6)	10.7 (9.4–13.6)	11.5 (9.1–14.9)	0.36
Temperature (F)	98.2 (97.9–99.3)	98.8 (98.4–100.5)	99.3 (98.4–101.1)	0.007
Pulse	114 (97–129)	121 (100–146)	126 (110–146)	0.029
Respiration Rate	24 (20–26)	24 (20–28)	24 (20–28)	0.33

Univariate analysis performed using Kruskal-Wallis for continuous variables and Pearson Chi Square test for dichotomous variables. Values presented represent the median with the 25–75 percentiles, except where noted.

* denotes significant value (P < 0.05).

Table 3

Odds ratios for Model 2 Predictive Variables

Predictor	Odds Ratio *	95% Confidence Interval	p value
CRP	1.30 **	1.19 – 1.42	<0.001
Pulse @ 97°	1.31	1.05 – 1.63	0.018
Pulse @ 99°	1.09	0.96 – 1.25	0.19
Pulse @ 101°	0.92	0.76 – 1.10	0.36
Pulse @ 103°	0.77	0.56 – 1.05	0.10

* Odds ratios greater than 1 mean that increases in the predictor variable correlate with increased infection severity

** Represents the association between outcome and a 10 unit increase in CRP (mg/L)

Table 4

Effect of Varying CRP in the Predictive Model

CRP (mg/L)	Predicted Probability of Infection (%)	Predicted Probability of Disseminated Infection (%)
20	63.5	30.0
30	69.4	35.9
40	74.7	42.2
50	79.4	48.8
60	83.4	55.4
70	86.7	61.8
80	89.5	67.8
90	91.7	73.3
100	93.6	78.1
110	94.9	82.4
120	96.1	85.9
130	97.0	88.8
140	97.7	91.2
150	98.2	93.1
160	98.6	95.8
170	98.9	96.8
180	99.1	97.4
190	99.4	98.1
200	99.5	98.5

Percentages determined based on varying CRP within Model 2 while holding all other variables constant at their median values.

Table X

Patient outcomes

	Inflammation (n=47)	Local Infection (n=41)	Disseminated Infection (n=103)	p-value*
Length of Stay (days)	0.57 (0.25–1.02)	2.93 (1.94–4.40)	5.78 (3.93–9.55)	<0.001
Operations	0 (0–0)	0 (0–1)	1 (1–2)	<0.001
ICU Admission (%)	0	4.9	10.6	0.047
Antibiotic Duration (days)	0 (0–0)	14 (10–28)	32 (21–42)	<0.001
Days with Fever	0 (0–0)	0 (0–1)	1 (0–3)	<0.001

Univariate analysis performed using Kruskal-Wallis for continuous variables and Pearson Chi Square test for dichotomous variables. Values presented represent the median with the 25–75 percentiles, except where noted.

* denotes significant value (P 0.05).