A Novel Classification System Based on Dissemination of Musculoskeletal Infection is Predictive of Hospital Outcomes

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Background: Musculoskeletal infections (MSKIs) are a common cause of pediatric hospitalization. Children affected by MSKI have highly variable hospital courses, which seem to depend on infection severity. Early stratification of infection severity would therefore help to maximize resource utilization and improve patient care. Currently, MSKIs are classified according to primary diagnoses such as osteomyelitis, pyomyositis, etc. These diagnoses, however, do not often occur in isolation and may differ widely in severity. On the basis of this, the authors propose a severity classification system that differentiates patients based on total infection burden and degree of dissemination.

Methods: The authors developed a classification system with operational definitions for MSKI severity based on the degree of dissemination. The operational definitions were applied retrospectively to a cohort of 202 pediatric patients with MSKI from a tertiary care children's hospital over a 5-year period (2008 to 2013). Hospital outcomes data [length of stay (LOS), number of surgeries, positive blood cultures, duration of antibiotics, intensive care unit LOS, number of days with fever, and number of imaging studies] were collected from the electronic medical record and compared between groups.

Results: Patients with greater infection dissemination were more likely to have worse hospital outcomes for LOS, number of surgeries performed, number of positive blood cultures, duration of antibiotics, intensive care unit LOS, number of days with fever, and number of imaging studies performed. Peak C-reactive protein, erythrocyte sedimentation rate, white blood cell count, and temperature were also higher in patients with more disseminated infection.

Conclusions: The severity classification system for pediatric MSKI defined in this study correlates with hospital outcomes and markers of inflammatory response. The advantage of this classification system is that it is applicable to different types of MSKI and represents a potentially complementary system to the previous practice of differentiating MSKI based on primary diagnosis. Early identification of disease severity in children with MSKI has the potential to enhance hospital outcomes through more efficient resource utilization and improved patient care.

Level of Evidence: Level II—prognostic study.

Key Words: musculoskeletal infection, osteomyelitis, septic arthritis, pyomyositis

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Musculoskeletal infection (MSKI) is a common cause of hospitalization in the pediatric population.[1] Although long-term morbidity and mortality associated with adequately treated MSKI is relatively low, some children develop severe disease with systemic complications and/or permanent disability. Improved methods that allow for accurate stratification of MSKI severity could improve patient outcomes and maximize resource utilization.

Presently, most orthopaedic surgeons break down MSKI into individual diagnostic categories such as osteomyelitis, pyomyositis, septic joint, etc.[2] The inherent limitation with this classification system is that the clinical presentations, treatments, and prognoses are highly variable within each of these groups.[3] Moreover, published data suggest that pediatric MSKI is rarely isolated to a single tissue, but rather is a spectrum of infection involving a combination of bone, muscle, and joint tissue.[1,4] The lack of a useful severity stratification system is a perceived barrier to the efficient diagnosis and optimal management for children with MSKI.

The authors propose a stratification system that differentiates patients with MSKI based on severity of infection and degree of dissemination. Similar risk-stratification systems

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reflective of total disease burden or injury have proven useful in tumor staging and polytrauma grading systems.[5–8] This severity stratification system represents a novel approach to pediatric MSKI that has the potential to complement the preexisting classification model by anatomic location. In this paper, the authors describe a 3-tiered severity stratification system and test the hypothesis that this system effectively predicts important hospital outcomes.

METHODS

An IRB-approved retrospective review was conducted to identify patients aged 0 to 18 who presented to the pediatric emergency room at a tertiary care children's hospital with concern for MSKI and received orthopaedic consultation over a 5-year period (2008 to 2013). Patients with posttraumatic infection, postoperative infection, poststreptococcal disease (included poststreptococcal reactive arthritis and acute rheumatic fever), chronic recurrent multifocal osteomyelitis or other chronic infectious processes (eg, fungal or mycobacterial infection), necrotizing fasciitis, and cellulitis were excluded.

The authors developed a 3-tiered stratification system of pediatric MSK infection that separated patients into inflammation, local infection, and disseminated infection groups based on operational definitions developed in collaboration with radiologists, pediatric infectious disease specialists, and pediatric hospitalists (see Table 1 for detailed descriptions of the operational definitions of infection severity and Fig. 1 for representative imaging from each category). The absence of positive culture or positive imaging resulted in a classification of "inflammation." Imaging characteristic of infection in 1 anatomic site or a single positive culture led to classification as "local infection." "Disseminated infection" was defined as the presence of multiple positive blood cultures, positive tissue cultures from different anatomic sites, imaging characteristic of infection in multiple anatomic sites, and/or thromboembolic disease. Orthopaedic surgeons evaluated the imaging used for these definitions for the presence of osteomyelitis or pyomyositis. Septic arthritis was always identified with arthrocentesis. The criteria delineated in the severity stratification system were applied retrospectively to the patient cohort in the study. In addition, patients were classified based on operational definitions for infection anatomy. The criteria for the anatomic operational definitions are listed in Table 2 and a consort diagram of inclusion and exclusion criteria for each group is displayed in Figure 2.

To validate the severity classification system, hospital outcomes data were collected including length of stay (LOS) (days), number of surgeries performed, number of positive blood cultures, total duration of antibiotics (days), length of intensive care unit (ICU) stay, number of days with fever (defined as $>101.5^{\circ}$F), and number of imaging studies performed (ultrasound, x-rays, magnetic resonance imaging, and computed tomographic scan). Markers of inflammation such as peak C-reactive protein (CRP, mg/L), erythrocyte sedimentation rate (ESR, mm/h), white blood cell count (WBC, thou/μL), and temperature ($^{\circ}$F) were also recorded.

TABLE 1. Operational Definitions of Infection Severity

	Definition	Example
Inflammation	All of the following (if available) must be true: Negative local culture Negative blood culture The criteria for local or disseminated infection are not met	Transient synovitis
Local infection	One of the following must be true: Imaging diagnostic for osteomyelitis or pyomyositis in 1 anatomic site Local culture positive AND/OR fluid/tissue consistent with infection* One positive blood culture The criteria for disseminated infection are not met	Isolated distal femoral osteomyelitis with no subperiosteal abscess Isolated septic hip
Disseminated infection	For 2 or more anatomic sites, at least one of the following must be true: Imaging diagnostic for osteomyelitis or pyomyositis Local culture positive AND/OR fluid/tissue consistent with infection* Two or more positive blood cultures Thromboembolic disease	Distal fibular osteomyelitis with subperiosteal abscess Septic hip with surrounding muscle pyomyositis

*Grossly purulent, cell count >50,000, positive culture includes positive PCR.

Statistical Methods

Univariate analyses were performed to assess for significant differences between the groups using Kruskal-Wallis tests for continuous variables and χ^2 tests for dichotomous variables. Comparisons between 2 groups were performed using Mann-Whitney's U test because of nonparametric distributions and small sample sizes. Data analysis was performed using the statistical analysis tool GraphPad Prism version 6 (LaJolla, CA). P-values ≤ 0.05 were considered significant.

RESULTS

There were 273 pediatric orthopaedic consultations for suspected MSKI from the emergency department during the study period. Of these, 202 (74%) met the study criteria and were included. Among the final study population, 52 (26%) children had inflammation, 46 (23%) had local infection, and 104 (51%) had disseminated infection. There were no significant differences among the groups by age, sex, ability to bear weight, or history of trauma. However, patients with more severe infection were more likely to have seen a physician before presentation (Table 3).

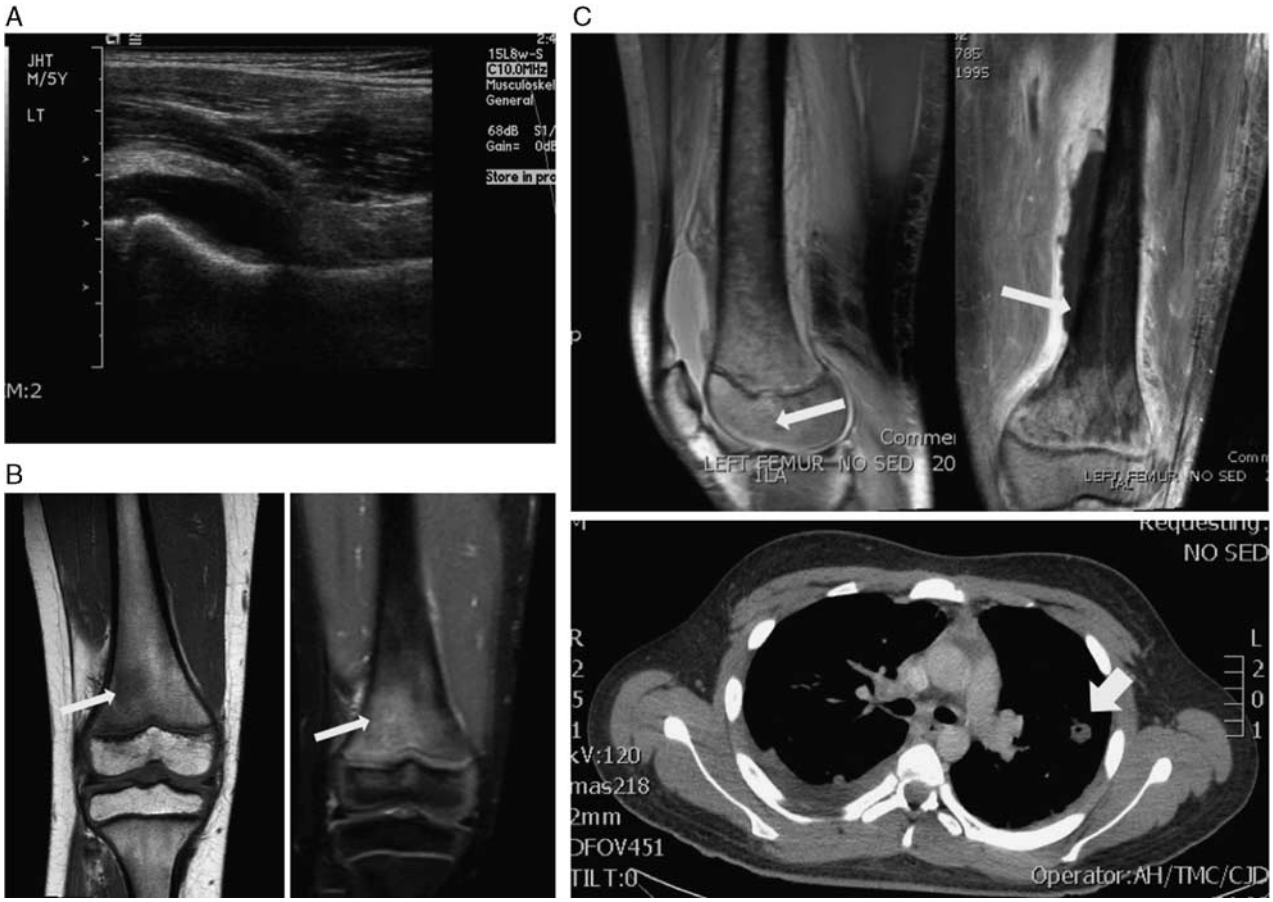

FIGURE 1. Imaging of pediatric musculoskeletal disease. Representative magnetic resonance imaging (MRI), computed tomographic, and ultrasound images for the different types of infection severity are represented in this study. A, An ultrasound from a patient with transient synovitis who is categorized as having inflammation. B, An MRI of a patient with isolated distal femoral osteomyelitis (see arrows) who falls into the local infection category of disease severity. C, A patient with distal femoral osteomyelitis and a subperiosteal abscess based on MRI imaging (see arrows in higher image), as well as a septic pulmonary embolus that was found on chest CT (see arrow in lower image). This patient was categorized as having disseminated infection.

To validate the efficacy of the severity stratification system, patient outcomes were compared across groups. Patients stratified into a more severe group were more likely to have worse outcomes for LOS, number of surgeries performed, number of positive blood cultures, duration of antibiotics, ICU LOS, number of days with fever, and number of imaging studies performed during the hospital stay (Table 4). Hospital outcomes for LOS and duration of posthospitalization antibiotics for each group are represented graphically in Figure 3. Peak CRP, ESR, WBC, and temperature were also higher in patients stratified into a more severe infection category (Table 5).

Different MSKI by anatomic site for each of the groups are defined in Table 6. The disseminated group consisted mainly of complex disease and pyomyositis, whereas local infections were largely composed of superficial abscess, septic joint, and osteomyelitis.

Bacteria isolated by blood and/or tissue culture for each severity category are listed in Table 7 *Staphylococcus aureus* was the most prevalent organism causing infection in both the local and disseminated groups, causing 58% and 66% of infections, respectively.

Anatomic locations of infection for each severity group are represented in Figure 4 and listed in Table 8. The hip and knee were the most common anatomic locations for infection in all 3 of the severity groups.

DISCUSSION

This study demonstrates that a 3-tiered severity stratification system of pediatric MSKI correlates with hospital outcomes and markers of inflammatory response. This stratification system is applicable to different types of MSKI and is complementary to the current paradigm of differentiating MSKI based on primary anatomic involvement.

Prior studies have demonstrated that systemic dissemination of infection is associated with complications that contribute to worse hospital outcomes. Mignemi et al[9] determined that children with severe MSKI who

TABLE 2. Operational Definitions for Anatomic Diagnosis

Diagnosis	Definition	Example
Tissue injury of unknown origin	Diagnosis of exclusion Negative tissue and/or blood culture Joint effusion	Transient synovitis of the hip
Superficial abscess	Superficial to deep fascia of limb, or located in hand or foot*	Septic prepatellar bursitis, superficial forearm abscess
Septic joint	Limited to joint space only with no extension into surrounding muscle or bone Synovial aspirate grossly purulent, > 50,000 cells, positive gram stain, and/or positive bacterial culture	Septic knee
Osteomyelitis	Isolated to bone only, no extension into subperiosteal space or surrounding muscle/joint	Proximal femur osteomyelitis
Deep abscess/pyomyositis	Deep to fascia of limb Isolated to muscle only, no extension into nearby bone or joint May include multiple muscle groups May be mild (edema only), moderate (phlegmon), or severe (abscess)	Obturator internus pyomyositis, adductor, and rectus femoris pyomyositis
Complex	Involving a combination of bone, muscle, and/or joint	Subperiosteal abscess, pericapsular pyomyositis with ischial osteomyelitis, clavicular osteomyelitis with supraclavicular abscess

*One patient in this series had an abscess in the gluteus maximus; however, there was no surrounding edema in the musculature and thus the patient was diagnosed with abscess rather than pyomyositis.

develop systemic involvement are more likely to develop coagulopathy. In a study by Hollmig and colleagues, 11/212 (5.2%) patients with osteomyelitis developed venous thromboembolism, which is evidence of disseminated infection. These patients were more likely to have a longer hospital stay, have more admissions to the ICU, and require more surgical procedures than those without DVT.[10] In addition, Gafur et al[1] previously identified a "hierarchy of tissue involvement" for MSKI severity that determined that patients with acute hematogenous osteomyelitis had worse outcomes than patients with pyomyositis or abscess. The results of this study are in accordance with that proposed hierarchy, as acute hematogenous osteomyelitis was significantly more likely to be in the disseminated group versus the local group (64% vs. 19%, $P < 0.0001$) than other types of infection.

Use of the proposed MSKI severity classification system could improve prognosis for children by more readily identifying patient that may require more aggressive medical management. However, decision making regarding procedural or surgical intervention (ie, for septic joint) will require case-by-case evaluation based on the anatomic diagnosis of infection. The elevated acute phase response with more severe disease observed in this study (CRP, ESR, WBC) suggests that acute inflammatory markers measured early in the hospital course may be an effective predictor of infection severity. This finding is in accordance with several other studies that have identified elevated CRP as an indicator of more severe disease.[10–14]

A study by Copley et al[13] developed a scoring system that assessed severity of illness in pediatric patients with osteomyelitis based on initial CRP, CRP at 48 and 96 hours, and several other clinical characteristics. Although Copley's study accurately stratifies patients to predict clinical outcomes, the severity classification system

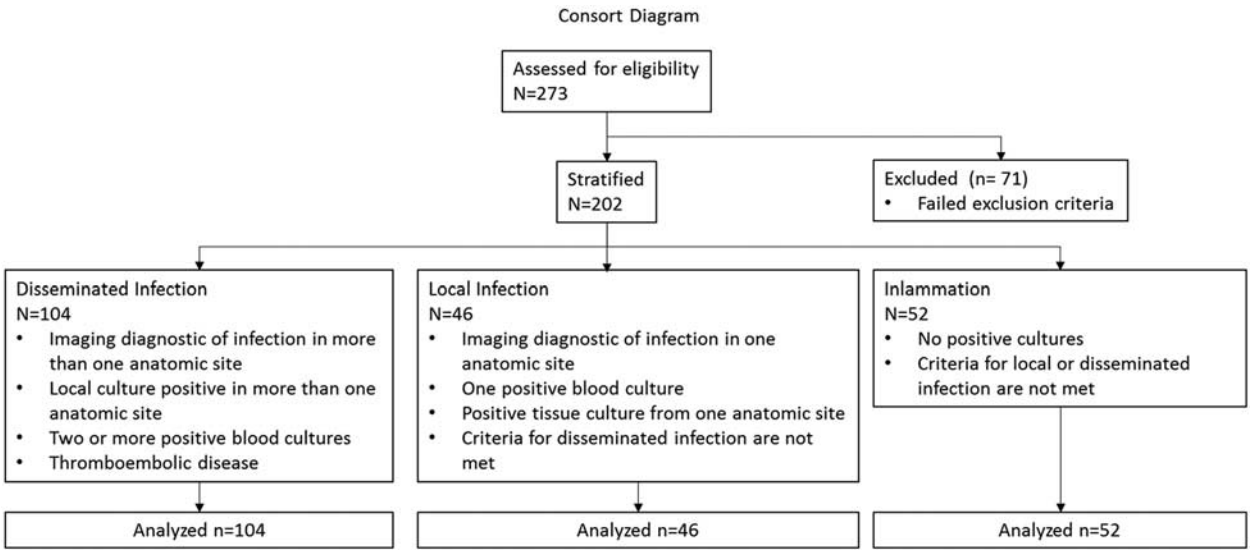

FIGURE 2. Consort diagram of operational definitions. Inclusion and exclusion criteria for each of the operational definition categories displayed in consort diagram format.

TABLE 3. Results of Univariate Analysis for Pediatric Musculoskeletal Infection by Classification

	Inflammation (n = 52)	Local Infection (n = 46)	Disseminated Infection (n = 104)	N	H/χ^2	*df*	*P*
Epidemiologic data							
Age (y)	4.95 (3.25-6.68)	4.99 (1.88-10.65)	6.35 (2.96-10.28)	202	3.134	2	0.21
Sex (M:F)	35:17	29:17	62:42	202	0.885	2	0.64
Non–weight-bearing at presentation (%)	57.7	63.0	68.3	202	1.74	2	0.42
History of trauma (%)	21.1	15.2	24.0	202	1.48	2	0.48
Previously seen by MD (%)	53.8	76.1	86.5	202	20.17	2	< 0.0001*

Univariate analysis performed using Kruskal-Wallis test for continuous variables and χ^2 test for dichotomous variables. Comparisons performed using Dunn's test. Values presented represent the median and the 25th to 75th percentile range, except where noted.
*Significant value ($P \leq 0.05$).
df indicates degrees of freedom; H, Kruskal-Wallis statistic.

TABLE 4. Outcomes by Severity Classification

	Inflammation (n = 52)	Local (n = 46)	Disseminated (n = 104)	*P*	Comparisons	*P*
Inpatient hospital outcomes						
Length of stay (d)	0.43 (0.25-1.01)	2.91 (1.94-4.30)	5.77 (3.94-9.53)	< 0.0001*	Inflammation vs. local	< 0.0001**
					Inflammation vs. disseminated	< 0.0001**
					Local vs. disseminated	< 0.0001**
No. surgeries performed	0 (0-0)	0 (0-1)	1 (1-2)	< 0.0001*	Inflammation vs. local	< 0.0001**
					Inflammation vs. disseminated	< 0.0001**
					Local vs. disseminated	< 0.0001**
No. positive blood cultures	0 (0-0)	0 (0-0)	0 (0-2)	< 0.0001*	Inflammation vs. local	0.0427**
					Inflammation vs. disseminated	< 0.0001**
					Local vs. disseminated	0.0003**
Duration of antibiotics (d)	0 (0-0)	14 (10-28)	31.5 (21.5-42.0)	< 0.0001*	Inflammation vs. local	< 0.0001**
					Inflammation vs. disseminated	< 0.0001**
					Local vs. disseminated	< 0.0001**
% patients with ICU admission (n)	0 (0)	4.3 (2)	9.6 (10)	0.0496*	Inflammation vs. local	0.2178
					Inflammation vs. disseminated	0.0313**
					Local vs. disseminated	0.3454
No. days with fever (> 101.5°F)	0 (0-0)	0 (0-1)	1 (0-3)	< 0.0001*	Inflammation vs. local	0.0053**
					Inflammation vs. disseminated	< 0.0001**
					Local vs. disseminated	< 0.0001**
No. MRIs performed	0 (0-0)	0 (0-1)	1 (1-2)	< 0.0001*	Inflammation vs. local	0.0012
					Inflammation vs. disseminated	< 0.0001**
					Local vs. disseminated	< 0.0001**
No. ultrasounds performed	1 (0-1)	0 (0-1)	1 (0-2)	0.0088*	Inflammation vs. local	0.1216
					Inflammation vs. disseminated	0.0903
					Local vs. disseminated	0.0042**
No. CTs performed	0 (0-0)	0 (0-0)	0 (0-0)	0.0023*	Inflammation vs. local	0.5953
					Inflammation vs. disseminated	0.0034**
					Local vs. disseminated	0.0292**
No. x-rays performed	1 (1-3)	1 (1-2)	2 (1-4)	< 0.0001*	Inflammation vs. local	0.2575
					Inflammation vs. disseminated	0.0033**
					Local vs. disseminated	0.0002**

Univariate analysis performed using Kruskal-Wallis/Mann-Whitney *U* test for continuous variables and χ^2/Fisher's exact test for dichotomous variables. Quantitative values represent the median with 25th to 75th percentile interquartile range in parentheses, except where noted otherwise.
CT indicates computed tomography; ICU, intensive care unit; MRI, magnetic resonance imaging.
*Significant value ($P \leq 0.05$) as determined by Kruskal-Wallis test or χ^2 test.
**Significant value ($P \leq 0.05$) as determined by Mann-Whitney *U* test or Fisher's exact test.

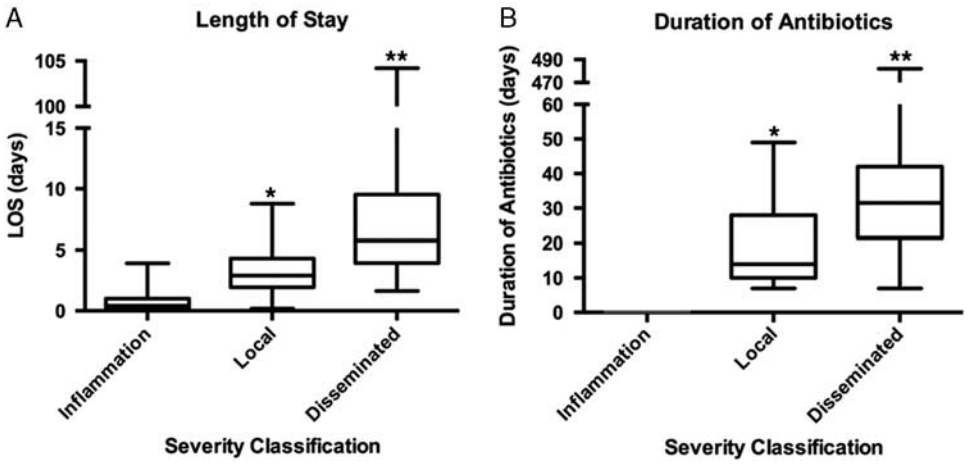

FIGURE 3. Duration of length of stay and antibiotics for severity groups. Standard box-and-whisker plots of length of stay (LOS) (A) and posthospitalization duration of antibiotics (B) for different severity groups. *Statistically significant differences ($P < 0.05$) between the local severity group and the other 2 groups. **Statistically significant differences ($P < 0.05$) between the disseminated group and the other 2 groups.

TABLE 5. Peak Laboratory Values During Hospitalization

	Inflammation (n = 52)	Local Infection (n = 46)	Disseminated Infection (n = 104)	N	H/χ^2	*df*	*P*
Peak laboratory values							
CRP peak (mg/L)	5.30 (2.25-17.75)	53.80 (23.70-89.33)	110.8 (59.63-232.7)	202	100.1	2	< 0.0001*
ESR peak (mm/h)	15.00 (11.00-30.00)	36.00 (17.75-71.25)	70.00 (45.25-92.00)	201	78.25	2	< 0.0001*
WBC peak (thou/μL)	11.45 (8.65-13.65)	10.70 (9.20-14.80)	12.90 (10.55-17.13)	199	10.29	2	0.0058*
Temperature peak (°F)	98.6 (98.2-99.3)	100.4 (98.9-102.3)	102.7 (100.8-103.3)	198	68.47	2	< 0.0001*

Univariate analysis was performed using Kruskal-Wallis test for continuous variables.
Values presented represent the median and the 25th to 75th percentile range.
*Significant value ($P \leq 0.05$).
df indicates degrees of freedom; H, Kruskal-Wallis statistic.

TABLE 6. Specific Diagnoses for Each Severity Group

	Diagnosis	n (%)
Inflammation (N = 52)	Tissue injury of unknown origin	52 (100)
Local (N = 46)	Superficial abscess	22 (48)
	Septic joint	11 (23)
	Osteomyelitis	9 (20)
	Pyomyositis	4 (9)
Disseminated (N = 104)	Complex disease*	84 (81)
	Pyomyositis	17 (16)
	Osteomyelitis	2 (2)
	Superficial abscess	1 (1)

*Complex disease includes multiple diagnoses, for example, septic arthritis with osteomyelitis.

TABLE 7. Causative Organism by Infection Severity

	Microbe	n (%)
Inflammation (N = 52)	Negative	26 (50)
	Not performed	26 (50)
	Total	52 (100)
Local (N = 46)	*Staphylococcus aureus*	30 (66)
	Streptococcus pneumoniae	1 (2)
	Mixed gram positive/negative	1 (2)
	Salmonella species	1 (2)
	Negative	13 (28)
	Total	46 (100)
Disseminated (N = 104)	*Staphylococcus aureus*	60 (58)
	Streptococcus pyogenes	11 (11)
	Kingella kingae	3 (3)
	Bartonella henselae	2 (2)
	Kocuria varians	1 (1)
	Salmonella species	1 (1)
	Stahylococcus epidermidis	1 (1)
	Streptococcus agalactiae	1 (1)
	Streptococcus pneumoniae	1 (1)
	Gram-negative rods	1 (1)
	Negative	22 (21)
	Total	104 (100)

in the current study is applicable to MSKIs beyond the subset of children with osteomyelitis. Further analysis will be necessary to determine whether the magnitude of the acute phase response at admission accurately predicts severity classification as defined in this study.

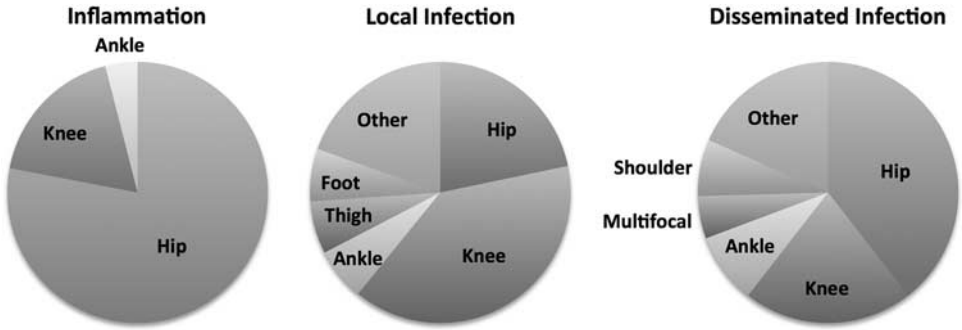

FIGURE 4. Anatomic locations of infection. Distribution of anatomic locations of infection by severity group represented graphically. Refer to Table 8 for additional information.

The limitations of this study are similar to those of any retrospective review. Treatment protocols for each patient varied by the treating physicians involved in the patients' care. In addition, diagnostic imaging and culture results were not available for all the patients in the study. This is evident in the different diagnostic workup panels performed for patients in different severity groups (Table 9). These discrepancies may have introduced biases into the statistical analysis, as some patients in the local group that did not undergo advanced imaging may have been identified as having disseminated infection with magnetic resonance imaging or computed tomographic evaluation. In the statistical analysis, confounding variables were not controlled for in the univariate analyses comparing the different stratification groups. Follow-up data were not included in this analysis, as the goal of the study was to look specifically at factors present at the time of admission and outcomes limited to the immediate hospital stay.

The goal of this study was to develop and test a severity stratification system of pediatric MSKI that may potentially be useful for improving in-hospital and long-term outcomes. Early differentiation between MSKIs of different severities would allow for more effective utilization of hospital resources. If the inflammation group can be rapidly identified and triaged, they can receive outpatient care through their primary care provider or in the emergency department. Expeditious recognition and treatment of local infection, through rapid imaging, antibiotics, and surgical debridement when necessary, would prevent this group of children from progressing to disseminated disease. However, further validation studies will be required to determine the utility of these operational definitions in a clinical setting.

The stratification system proposed in the current study is unique in that it offers an approach pediatric MSKI based on the degree of systemic involvement, regardless of the type of infection or causative bacteria.

TABLE 8. Anatomic Locations of Infection

	Location	n (%)
Inflammation (N = 52)	Hip	40 (77)
	Knee	10 (19)
	Ankle	2 (4)
	Total	52 (100)
Local infection (N = 46)	Knee	18 (39)
	Hip	10 (22)
	Ankle	3 (7)
	Thigh	3 (7)
	Foot	3 (7)
	Hand	2 (4)
	Leg	2 (4)
	Elbow	2 (4)
	Wrist	1 (2)
	Forearm	1 (2)
	Shoulder	1 (2)
	Total	46 (100)
Disseminated infection (N = 104)	Hip	42 (40)
	Knee	20 (19)
	Multifocal	10 (10)
	Ankle	9 (9)
	Shoulder	7 (7)
	Foot	4 (4)
	Wrist	4 (4)
	Elbow	2 (2)
	Spine	2 (2)
	Thigh	1 (1)
	Arm	1 (1)
	Clavicle	1 (1)
	Leg	1 (1)
	Total	104 (100)

Hip and pelvis defined as SI joint, pelvis, hip joint, proximal one-third femur, thigh—middle one-third femur, knee—distal one-third femur, knee joint, proximal one-third tibia, leg—middle one-third tibia, ankle—distal one-third tibia, ankle joint, hindfoot, foot—mid and forefoot, shoulder—shoulder girdle, shoulder joint, proximal one-third humerus, arm—middle one-third humerus, elbow—distal one-third humerus, elbow joint, proximal one-third radius/ulna, forearm—middle one-third of radius/ulna, wrist—distal one-third radius/ulna, wrist joint, carpus, hand—metacarpals and phalanges.

Anatomic sites include surrounding muscle and soft tissue.

TABLE 9. Diagnostic Studies by Classification

No. Patients Who Received	n (%)		
	Inflammation	Local	Disseminated
MRI	8 (15)	18 (40)	100 (96)
CT	1 (2)	3 (7)	19 (18)
X-ray	51 (98)	42 (93)	99 (95)
Ultrasound	35 (67)	22 (49)	70 (67)
Blood culture	23 (44)	40 (89)	103 (99)
Tissue culture	6 (12)	36 (80)	90 (86)

CT indicates computed tomography; MRI, magnetic resonance imaging.

This method of stratification also has utility in clinical research because it allows unambiguous classification and outcome comparisons for all pediatric MSKI. Analysis of MSKI data from additional institutions will be necessary to confirm that the operational definitions in this study are widely applicable.

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