ORIGINAL ARTICLE

DIAGNOSTIC DILEMMAS OF PEDIATRIC OSTEOARTICULAR INFECTIONS AND SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

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Abstract

Objective and Aim: Delayed diagnosis of pediatric osteoarticular infections at initial presentation can lead to serious sequelae. Osteoarticular infections can be classified into categories dependent on presence of a septic joint or associated abscesses (simple or complex). A third group is identified; complex with systemic inflammatory response syndrome (SIRS). These patients are clinically unstable and require intensive care. The aim of the study was to determine factors associated with delayed care in patients with osteoarticular infections to prevent SIRS.

Methods and Materials: Retrospective chart review was conducted for various clinical parameters. Patients were classified into groups depending on magnetic resonance imaging (MRI) and clinical findings. Only infections requiring surgery were included. These fell into two categories: (1) complex clinically stable (non-SIRS) and (2) complex clinically unstable (SIRS). Factors associated with each group were analyzed.

Results: Common clinical features observed were increasing pain in 33 (100%) patients, decreased ambulatory status with lower extremity infections in 28 (100%) patients, soft tissue swelling in 16 (48.5%) patients. Four patients were in the SIRS group and 29 patients were in the non-SIRS group. Time from symptom presentation to the first medical contact averaged 3 days in both the groups (p=0.7367). Time from symptom onset to Emergency Department (ED) presentation averaged 2 days in the SIRS group and 1 day in the non-SIRS group (p=0.0717). Average number of medical contacts before diagnosis was 4 in the SIRS group and 3 in the non-SIRS group (p=0.0091). Time from onset of symptoms to operating room was 11.5 days in the SIRS group and 5 days in the non-SIRS group (p=0.0170). Hospital length of stay was 5 days for the clinically stable group and 12.5 days for SIRS group (p=0.0078). Higher CRP, higher ESR and higher body temperature were observed in the SIRS group as compared to non-SIRS group which was statistically significant. White cell count was similar in both the groups. Methicillin resistant staphylococcus aureus was isolated in 75% of patients in the SIRS group and Methicillin sensitive staphylococcus aureus was isolated in 55.2% of patients in the non-SIRS group.

Conclusion: Children with progressive osteoarticular pain should be considered for an infection with a low threshold for obtaining laboratory tests and an MRI. The goal is to halt progression of infection, complications, and need for hospitalization. Though most patients present to the 1st medical contact in time, further medical contacts and presentation to ED is usually delayed in patients with SIRS.

Keywords: Diagnosis, Pediatric, Osteoarticular Infection, SIRS.

Introduction

Acute pediatric osteoarticular infections frequently have delayed diagnosis at initial presentation and can lead to serious sequelae which include permanent disability. (1-4) In an era of increasingly prevalent methicillin-resistant staphylococcus aureus (MRSA) infections, delayed diagnosis can lead to Systemic Inflammatory Response Syndrome (SIRS) within a matter of days. (5-7) In order to improve patient care in primary care settings and obviate dangerous delays, current clinical pathways must be optimized. (8, 9-11)

This study was conducted to identify and understand causes of delayed diagnosis of pediatric osteoarticular infections at a single institution with multiple pediatric orthopedists. Since infections are becoming progressively more complex with time, changing current treatment paradigms is necessary. (6) Currently, there are many classification systems for these infections. (12) For this study, the infections are divided into two classification types. Simple infections are characterized by osteomyelitis without an adjacent abscess; these can be treated with antibiotics. This type of infection will not be reviewed in this paper. Complex infections are characterized by osteomyelitis with sub-periosteal abscess or septic arthritis; these require debridement in the operating room (OR). When complex infections become even more severe, patients can develop SIRS or septic shock, requiring intensive care. (12-14) Pediatric SIRS criteria is defined as any two of the following (one of which must include abnormal temperature or white blood cell count): core temperature > 38.5°C or < 36°C; abnormal heart rate: >2 standard deviations above normal for age, or <10th percentile for age if child is <1 year; increased respiratory rate >2 standard deviations above normal for age, or mechanical ventilation for acute lung disease; abnormal white blood cell count, above or below normal for age, or >10% immature forms. (15)

Without warning, these patients can rapidly deteriorate to fulminate SIRS. This can be compared to falling off a cliff. This can lead to further complications including multifocal infections, deep vein thrombosis (DVT) or pulmonary distress, requiring intensive care and monitoring. (12, 16-18) Thus, patients with complex infections should be classified into two distinct categories: (1) complex clinically stable (e.g. complex infections without associated SIRS/sepsis) and (2) complex clinically unstable (e.g. complex infections with SIRS/sepsis). The goal of this paper is to identify obstacles that delay diagnosis so they may be rectified to prevent progression of complex infections.

Methods & Materials

A retrospective chart review of 33 patients with complex osteomyelitis with 35 infections, aged 4 months to 16 years and 9 months was conducted. All patients were admitted to Atlantic Health Hospitals between 2010 -2015. X-rays and magnetic resonance imaging (MRI) studies were performed on all patients. Patient charts were studied for clinical parameters

including: clinical symptoms; laboratory values at presentation (e.g. erythrocyte sedimentation rate [ESR; reference range 0-20 mm/hr], C- reactive protein [CRP; reference range 0.0-9.0 mg/L] and white blood cell count [WBC; reference range 4.50-11.00/nL]); vital signs at presentation (heart rate [HR; tachycardia defined as: >180 beats/min ages 0 days-1 year, >140 beats/min ages 2-5 years, >130 beats/min ages 6-12 years, and >110 beats/min ages 13-<18 years] and respiratory rate [RR; elevated rate defined at >34 breaths/min ages 1 month-1 year, > 22 breaths/min from 2-5 years, > 18 breaths/min from 6-12 years, and >14 breaths/min from 13-<18 years]); number of medical contacts until diagnosis; time from start of symptoms until first professional contact; time from symptoms to the OR; hospital length of stay (LOS); time from MRI to surgery; MRI findings; pathogen, and antibiotic usage. Patients were classified into groups depending on MRI and clinical findings. Only infections that required surgery were included in this study. These infections fell into two categories: (1) complex clinically stable (non-SIRS); (2) complex clinically unstable (SIRS). Factors associated with non-SIRS and SIRS group were compared.

Statistical Analysis: All variables were tested for normality. If the variable did not fail the normality test, a 2-sample t-test was used to calculate the p-value. All variables with a p-values followed by an * failed the normality test and was calculated with Mann-Whitney. P value of < 0.05 was considered as significant.

Results

Clinical features observed were increasing pain in 33 (100%) patients, decreased ambulatory status with lower extremity infections in 28 (100%) patients, soft tissue swelling in 16 (48.5%) patients, septic shock including tachycardia and increased respiratory rate in 4 (12.1%) patients, multifocal infections in 3 (9.1%) patients, septic emboli to skin in 2 (6.1%) patients, cellulitis in 2 (6.1%) patients and pulmonary edema in 1 (3%) patient. Initial temperature on presentation included average temperature 38^0 C (range 36.5^0C -40^0C) with 18 (54.5%) of patients afebrile on presentation. Seven (21.2%) patients had a normal CRP. Average initial CRP was 91.4 mg/L (3-255 mg/L). All patients had ESR >10 mm/hr and 21 (70%) of patients had ESR >40 mm/hr. Average initial ESR was 59.07 mm/hr (24-104 mm/hr). Nineteen (57.6%) patients had WBC >11/nL. Average initial WBC was 12.827/nL (5.7-24.4 /nL).

The time from symptom presentation to the first medical contact averaged 3.6 days (0-14 days). The time from symptom onset to presentation in the Emergency Department (ED) averaged 5.6 days (1-16 days). Average number of medical contacts before diagnosis was 3.5. Mean time from onset of symptoms to OR was 6.7 days (1-16 days). Average time from MRI to surgery averaged 14.4 hours (8 minutes-4 days). One patient progressed to SIRS in as few as 5 days from initial symptoms. MRI findings included: septic joint in 7 (21.2%) patients, septic joint including adjacent osteomyelitis in 5 (15.2%) patients and osteomyelitis with sub-periosteal abscess in 21 (63.6%) patients. Twenty-nine (87.9%) patients were classified into the complex clinically stable group (non-SIRS) and 4 (12.1%) patients were classified into the complex clinically unstable group (SIRS). Details of complex clinically unstable group is depicted in Table 1. A comparison of hospital LOS, time to presentation to first medical contact, time to ED, time to OR, number of medical contacts, initial laboratory parameters and temperature between the 2 groups is presented in Table 2. The pathogens isolated in the SIRS and non- SIRS groups are depicted in Table 3. Of the SIRS patients, 25% had methicillin sensitive staphylococcus aureus (MSSA) and 75% had MRSA pathogens. Antibiotic treatment ranged from 4 to 8 weeks. The follow-up period ranged from 1 month to 4 years.

Discussion

Aggressively diagnosing pediatric osteoarticular infections is essential for effective treatment and avoidance of SIRS. (2,11,19) A minimum of 2 to 3 medical contacts can be expected as part of care prior to diagnosis. In this series, there were more medical contacts prior to diagnosis especially in patients with SIRS. Other sources of treatment delay are identified in this study. Routine delays occur as parents wait for children's symptoms to resolve spontaneously before bringing symptoms to medical attention. In this case, the treatment timeframe is already truncated upon time to first medical contact. This places increasing pressure on the healthcare provider to quickly and accurately diagnose the condition. The primary care provider should have a high index of suspicion for infection and quickly obtain baseline inflammatory markers including CRP and ESR levels for patients who are nonresponsive to over-the-counter medication and have symptoms of prolonged and increasing limb pain. (20) They should be alert to early signs of SIRS and look for underlying causes. (8,13,15) These patients should be referred to orthopedic specialists as soon as possible. (8) The SIRS patients described here were appropriately referred to orthopedists, however the acuity of their illness was not recognized by these specialists early on. The orthopedist should have a low threshold for obtaining an MRI in this situation. (1,20,21) Our study shows that delays in diagnosis can occur at any point during the course of an infection, even during interaction with the health care system. Some delays are unavoidable, especially early on, but many occur due to misinterpretation of clinical information.

Delays in diagnosis can cause significant morbidity with progression to SIRS. Other outcomes of delayed diagnosis include: lengthy hospital stays, prolonged antibiotic therapy with concomitant complications, pathologic fractures, permanent disability, mortality, and decreased quality of life. (5,6,10,22-24) Once correctly diagnosed, appropriate protocols must be followed to treat the infection expeditiously and halt progression to avoid SIRS. (8)

This sheds light on the ramifications of misdiagnosis and emphasizes the need to educate medical personnel

Table 1: Details of Complex clinically unstable group

Presentation of SIRS patients	Joint	Osteo site	Organism	Hospital LOS	Days 1st symptoms to 1st contact	Days 1st Symptoms to ED visit	Days 1st symptoms to OR	Total contacts until dx	Presenting temperature (°C)	Initial CRP (mg/L)	Initial ESR (mm/hr)	Initial WBC (/nL)
Knee effusion and pain; Fever; Septic Emboli to skin; Antalgic gait	Knee	Femur	MRSA	23	2	14	15	3	38.3	132	67	10.0
Pain and swelling wrist; Fever	-	Radius	MRSA	6	7	9	9	4	39.0	218	66	12.8
Upper leg pain; Fever	-	Femur	MRSA	10	7	7	11	5	39.1	246	66	8.3
Pain, swelling leg; Non-weight bearing, Ring finger pain and swelling. Fever, septic emboli to skin	Knee	Tibia/ Phalynx	MRSA	15	3	10	11	4	40.0	255	79	12.5

Note: SIRS: Systemic Inflammatory Response Syndrome, LOS: length of stay, ED: Emergency Department, OR: operating room, Dx: diagnosis, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, WBC: white blood cell count

Table 2: Comparison of SIRS and non-SIRS groups

Parameters	(SIRS Group (n=4)	Non-SIRS Group (n=29) (range)	p-value
Hospital LOS (days)	12.5 (6-23)	5 (1-12)	0.0078
Time to presentation to first medical contact (days)	3 (2-7)	3 (0-14)	0.7367
Time to ED (days)	2 (1-3)	1 (0-2)	0.0717
Time to OR (days)	11.5 (9-15)	5 (1-16)	0.0170
Total number of medical contacts	4 (4-5)	3 (1-5)	0.0091
Initial temperature (°C)	39.1 + 0.698	37.89 + 1.092	0.0300
Initial ESR (mm/hr)	69.5 + 6.35	57.46 + 22.26	0.0390
Initial CRP (mg/L)	232 (132-255)	69.4 (3-171)	0.0035
Initial WBC (/nL)	10.87 + 2.13	13.097 + 5.199	0.1560

Note: SIRS: Systemic Inflammatory Response Syndrome, LOS: length of stay, ED: Emergency Department, OR: operating room, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: white blood cell count

Table 3: Pathogens isolated in SIRS and non-SIRS group

Pathogens	All patients	Complex Clinically Unstable (SIRS)	Complex Clinically Stable (non-SIRS)
Group A beta hemolytic streptococcus	3 (9.1%)	0	3
MRSA	7 (21.2%)	3	4
MSSA	17 (51.5%)	1	16
Kingella Kingae	1 (3%)	0	1
No Growth	5 (15.2%)	0	5
Total	**33**	**4**	**29**

Note: SIRS: Systemic Inflammatory Response Syndrome, MRSA: methicillin-resistant staphylococcus aureus, MSSA: methicillin-sensitive staphylococcus aureus

on accurate and timely use of diagnostic measures. Most primary care providers do not have extensive experience diagnosing and treating osteoarticular infections. Because of this, the appropriate diagnostic studies are not performed and there is an over reliance on plain radiographs. Perhaps some of these diagnostic delays may be unavoidable. (25)

There is also a failure by orthopedists to recognize the potential severity of these infections. In this small population, the 4 patients that required intensive care were seen by orthopedists earlier in their course. Perhaps more aggressive early intervention could have mitigated infection progression. A recent paper found that older age, temperature greater than 38.5°C and a higher CRP are predictors of complicated disease, however the authors stress the importance of diagnosis of these complex infections stating it is "preferable to set the cut-off low and 'over diagnose' complicated acute hematogenous osteomyelitis at initial presentation." (26). Similarly in our study, we found that patients who had SIRS had higher CRP, higher ESR and higher body temperature at the time of presentation.

There are many articles in the literature emphasizing the need for holding a high index of suspicion for osteoarticular infections in children. (2,6,8,10,20,27-29) However, there is still a lack of consensus regarding the appropriate diagnostic protocols to follow when these children present. (11) Enhanced awareness and increased vigilance, especially for signs of clinical instability, can assist with prompt diagnosis and lead to better outcomes. (11,13,15,25) The average CRP values for this study were ten times the upper limit of the normal range upon presentation. It is possible that this was due to delayed diagnosis in this population. A judicious use of laboratory testing, particularly with respect to inflammatory markers is needed. (29-31) In cases where the diagnosis is uncertain, MRI is a useful diagnostic tool. (27) Any clinical suspicion of osteomyelitis, regardless of laboratory results, should prompt the clinician to obtain an MRI. Any child with progressive pain in a bone or joint with increased disability independent of normal laboratory results should be considered for an osteoarticular infection with a very low threshold for obtaining an MRI. (19,20,21,32) In the era of MRSA and other aggressive pathogens, obtaining a negative MRI result should not be viewed as extraneous clinical information. (10,11,22,28,31) Since an MRI study can diagnose osteomyelitis within 24 hours of onset, it should be used with greater frequency. (1,15,33) This needs to be emphasized to primary care and emergency department clinicians.

This experience in a community hospital setting is applicable to many other community settings. Two high volume pediatric academic institutions reports the percentage of patients with MRSA osteomyelitis and septic arthritis at 34.8% and 51% respectively. (34,35) As the percentage of MRSA climbs, the severity of patients' illnesses will increase. (7) Similarly in our study though MSSA was the predominant pathogen isolated, 75% of patients who developed SIRS had MRSA infection. In this era of multi-drug resistant organisms, a more aggressive approach in identifying and treating such infections will decrease morbidity and reduce the likelihood of longer hospitalizations. (25)

It is unclear how many children without infections present with similar complaints to those with infections. A further confounder in this population, is that many children with osteomyelitis also have a history of trauma. These issues illustrate why clinicians must hold a high suspicion for infection; it can masquerade as more benign pathology, especially early on. A limitation of this study is that the timing of symptom presentation was self-reported by patients and their caregivers and could not be independently verified.

Conclusion

It is recommended that clinicians hold a high suspicion for pediatric osteoarticular infections at initial presentation, promoting the expeditious diagnosis to prevent serious sequelae. The goal is to start treatment as quickly as possible, thereby halting infection progression and mitigating the need for prolonged hospitalization. It is important to note that in this study, a delay in diagnosis did not cause progression to SIRS in every case though SIRS is seen in patients with higher CRP, higher ESR and higher body temperature at the time of presentation. It is difficult to discern which patients with complex infections will progress to SIRS.

Infection progression may also be dependent on the time of symptomatic presentation, aggressiveness of the pathogen, and other factors, such as the patient's immune system status. Aggressive treatment is critical since clinically stable children with complex infections can easily progress to SIRS. (25) Patients with MRSA tend to decompensate quickly and once they present, the clock is ticking for the clinician to appropriately identify the infection.

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