AN ASSESSMENT OF SEVERITY OF ILLNESS OF PEDIATRIC MUSCULOSKELETAL INFECTIONS: 1994-2009

by

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ABSTRACT

PURPOSE:

Care of children with osteomyelitis requires multi-disciplinary collaboration. This study evaluates the impact of evidence-based guidelines for pediatric osteomyelitis when applied by a multi-disciplinary team.

METHODS:

Guidelines for pediatric osteomyelitis were developed and implemented by a multi-disciplinary team comprised of orthopedics, pediatrics, infectious disease, nursing, and social work who met daily to conduct rounds and make treatment decisions. Children who were treated according to the guidelines (g) were compared to those who had been treated prior to the guidelines (ng) by retrospective review and statistical analysis.

RESULTS:

210 children of the 2002-2004 cohort (ng) were compared to 61 children of the 2009 cohort (g). No significant differences between the two cohorts were noted for age, race, gender, incidence of Methicillin-resistant *Staphylococcus aureus* (g=26.2%; ng=18.1%), incidence of Methicillin-sensitive *Staphylococcus aureus* (g=27.9%; ng=23.8%), bacteremia, or surgeries. Significant differences between cohorts were noted ($p<0.05$) for each of the following: timing of initial MRI (g=1.0 day; ng=2.5 days); clindamycin as initial antibiotic (g= 85.3%; ng=12.8%); blood cultures before antibiotic administration (g=91.8% ; ng=79.5%); tissue cultures from infection site (g=78.7%; ng=62.9%); identification of organism by tissue or blood culture (g=73.8%; ng=60.0%); antibiotic changes (g=1.4 changes; ng=2.0 changes); and mean oral antibiotic duration (g=43.7 days; ng=27.7 days). Children treated with guidelines had clinically important trends of a shorter total length of stay (g=9.7 days;

ng=12.8 days; p=0.054), and lower readmission rate (g=6.6%; ng=11.4%; p=0.34).

CONCLUSION:

Evidence-based treatment guidelines applied by a multi-disciplinary team resulted in more efficient diagnostic work-up, higher rate of identifying the causative organism, improved adherence to initial antibiotic recommendations with fewer antibiotic changes during treatment. Additionally, there were trends toward lower readmission rate and lower length of hospitalization. The establishment of evidence-based treatment guidelines will allow for the standardization of evaluation and treatment of children with musculoskeletal infections for severity of illness comparisons between cohorts separated through time and geographic location.

THE IMPACT OF EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES APPLIED BY A MULTI-DISCIPLINARY TEAM FOR THE CARE OF CHILDREN WITH OSTEOMYELITIS

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PRIOR PUBLICATIONS & PRESENTATIONS

PUBLICATIONS:

Copley LA, Kinsler A, Gheen T, Shar A, **Sun DQ**, Browne R. The Impact of Evidence-Based Clinical Practice Guidelines Applied by a Multi-Disciplinary Team for the Care of Children with Osteomyelitis. JBJS. **Accepted for Publication.**

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CHAPTER 1
An Introduction to Pediatric Musculoskeletal Infection (Osteomyelitis, Septic Arthritis, Pyomyositis)

Osteomyelitis is defined as an infection of bone and bone marrow with bacteria as the causative organism. Since bone in children is considered to be a highly vascular tissue, osteomyelitis most commonly occurs in the context of acute hematogenous spread after a transient episode of bacteremia.[1] Half of cases have been reported in children younger than 5 years of age.[2,3] Risk factors predisposing to osteomyelitis includes the male gender (boys twice more likely to be infected than girls) and immunocompromised state (eg: leukemia). [1] Trauma is reported in about 35% of children with osteomyelitis. Most cases of osteomyelitis occur in the metaphyseal region of long bones; infections of the femur, tibia, humerus account for 68% in one reported study. [4] Infections commonly involve only one location, with less than 10% of infections noted to be multifocal (involving two or more locations).[1]

Usually, osteomyelitis is due to a single causative organism. In older infants and children, *S. aureus* is the most commonly identified organism, accounting for more than half of cases.[5] Group A Streptococci, Group B Streptococci, and *E. coli* are also considered to be significant sources of hematogenous osteomyelitis in newborns and younger infants.[7] *S. pneumonia*e has been commonly isolated from children younger than 24 months of age.[8] *Salmonella* species commonly infect patients with sickle-cell disease, and *P. aeruginosa* is often identified in cases of osteochondritis after puncture wounds of the feet.[9,10]

Staphylococcus aureus can express adhesin proteins which are able to bind to an element of bone matrix and survive once internalized into osteoblasts.[11] Growing colonies of bacteria are then able to create protective biofilms and glycocalyx[12], making it increasingly difficult to eradicate the infection. If the infection is allowed to continue, chronic osteomyelitis is seen with cortical bone destruction by inflammatory cytokines, monocytes, and macrophages.[1] The necrotic bone can eventually separate and form a **sequestrum,** and new bone may form an incasing sheath surrounding the body of necrotic bone, known as an **involucrum**.[13]

Older children and adolescents often complain mostly of constant, well-localized pain at the site of infection along with fever. Infants and toddlers will present with irritability, limping, and refusal to bear weight on an extremity. Neonates can present with pseudoparalysis with significant tenderness of palpation at the affected site.[14] They usually have a history of a preceding fever. Neonates who are treated in an intensive newborn nursery and who require indwelling arterial and venous catheters are prone to develop multi-focal infections.[15]

Conventional radiographs are usually the first modality used in the work-up of suspected acute osteomyelitis. In the early stages, the radiographs are often normal; osteopenia is noted within 3-7 days of the infection[16] and requires at least 50% or more loss in bone density to be visible radiographically. It may take one or two weeks for this to unfold.[17] MRI with gadolinium-contrast has been reported to have an overall sensitivity of 97% for the detection of osteomyelitis and has become the modality of choice for patients with a strong suspicion

of osteomyelitis.[18,19] MRI is able to differentiate between bone and soft-tissue infections and facilitates the decision for surgery while informing the surgeon of the best surgical approach if surgery is indicated. Laboratory studies are supportive but not specific for the diagnosis of osteomyelitis. In a study performed on 44 children with acute hematogenous osteomyelitis, less than half (35%) of children had leukocytosis at the time of admission; however, inflammatory markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are elevated in more than 90% of children with deep infections.[20] CRP and ESR are also useful following monitoring the response to therapy. The identification of a causative organism is highly important not only for the purposes of diagnosis of the illness but also for guiding antibiotic selection. Blood cultures yield an organism in only 36%-55% of specimens whereas needle-aspiration of bone yields an organism in approximately 66% of cases.[21]

Septic Arthritis is a bacterial invasion of a joint space. If untreated, this condition may lead to irreversible joint damage. [1] The annual incidence varies between 2-10 per 100,000 in the general population.[22] Bacterial arthritis occurs due to hematogenous seeding following an episode of transient bacteremia, similar to osteomyelitis. The bacteria are able to enter the closed joint space and trigger an acute inflammatory **synovitis**, characterized by proliferative synovial lining-cell hyperplasia and the release of inflammatory cytokines and lysosomal enzymes, leading to cartilage degradation.[22] Bacteria are also able to enter the joint space through joint surgery, joint space aspirations, or direct puncture wounds from traumatic events. In children, it is also possible to have contiguous spread of osteomyelitis from an epiphysis or metaphysis to the adjacent joint space.

The organism isolated from a septic joint often varies with age. *S. aureus* is the most common cause of septic arthritis in all age groups combined. [23] There has been an increasing proportion of disease caused by community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA); CA-MRSA has been associated with complications such as venous thrombosis and pulmonary diseases when identified with osteomyelitis, but rarely in association with septic arthritis.[24-26] Various Streptococcal species may cause disease in children and include: Group A beta-hemolytic streptococci (children older than 4), Group B streptococci (children younger than three months), and *S. pneumonia*e (children younger than 2 years).[27,28] In children younger than 2-3 years of age, *Kingella kingae* has become an increasingly recognized cause of bacterial arthritis.[30] *N. gonorrhea* is recognized as a source in newborns and sexually-active adolescents.[31]

Septic arthritis presents with the abrupt onset of a red, hot, swollen and painful joint. The knee is often the most common site of infection, but hip infections are more commonly seen in young children.[2] An infected hip joint is often positioned in a flexed and externally rotated position with extreme pain elicited upon passive flexion and rotation of the hip. Polyarticular disease is seen in less than 10% of patients but is seen in up to 50% of patients infected with *N. gonorrhea*.[29] Systemic symptoms of disease, such as fever, malaise, and anorexia are seen in most pediatric populations; however, neonates may have less impressive symptoms due to an immature immune system.[1]

The definitive diagnosis of septic arthritis is the identification of bacteria in the synovial fluid. A clinical suspicion of joint sepsis should result in an immediate aspiration of joint fluid for bacterial culture. The synovial culture may be positive in only 40-50% of cases due to the inhibition of bacterial growth caused by joint fluid.[3] We are often limited to a presumptive diagnosis of gonococcal bacterial arthritis based on joint fluid nucleated cell count, characteristic signs/symptoms, laboratory inflammatory markers, and the indirect identification of the causative organism as may occur with positive blood cultures or, for example through the identification of *N. gonorrhea* from a genitourinary source, especially since gonococcus skin lesions and blood cultures rarely yield positive results.[32] PCR for bacterial DNA has been useful for the identification bacterial antigens in cases of culture-negative septic arthritis.[22]

Laboratory tests include: complete blood count with differential (CBC), CRP, and ESR measurements. Leukocytosis and elevated CRP and ESR levels may be seen in children with septic arthritis. Laboratory trends are helpful in monitoring the response to therapy.[13] In acute septic arthritis, plain radiographs do not initially demonstrate destructive joint lesions with characteristic juxta-articular osteoporosis and bone erosions taking weeks to manifest.[17] MRI and ultrasound are both more sensitive than plain radiographs in early septic arthritis. Ultrasound of the hip joint is commonly used and is able to detect joint effusions and guide needle insertion for aspiration whereas MRI can demonstrate adjacent osteomyelitis, soft-tissue edema and abscesses.[22]

Pyomyositis is described as a bacterial infection of skeletal muscle usually accompanied by abscess formation. This condition is common in tropical climates. However, it has been increasingly recognized as an entity in temperate climates with the first case reported in the United States in 1971.[33] Most cases of pyomyositis in the United States occur in the temperate climates during the warmest months of the year. Typically, pyomyositis begins with pain and swelling of the muscles. The muscles may become increasingly tender and indurated to the point of developing a "wooden" and firm texture upon palpation.[33] A unifying theory as to the pathogenesis of pyomyositis has not been clearly established; transient bacteremia combined with circulation to an area of injured muscle which may have a diminished resistance to bacterial infection may precede the development of pyomyositis. [34]

Although pyomyositis reports from the tropics describe the involvement of a single large muscle, 60% of cases in the United States describe multiple muscle involvement, most commonly the thighs, calves, gluteal, paraspinal muscles, psoas, latissimus dorsi, pectoralis, and the deltoids.[33] Pathology reports demonstrate edematous separations of myofibrils and muscle fibers with surrounding lymphocytosis. If left untreated, the disease progresses to the development of suppuration from bacteria and polymorphonuclear leukocytes.[13]

S. aureus is the predominant organism that is isolated from muscles in both tropical and temperate environments, accounting for 85% of cases in the United States and over 85% of

cases in the tropics.[3] *Clostridial* infections may lead to a fatal fulminant course of myonecrosis.[35]

The early diagnosis of pyomyositis is often difficult due to the fact that the inflamed muscle is deep and classic inflammatory signs are often not readily apparent in the surrounding soft tissue.[33] MRI scanning is invaluable for both disease localization and differentiation from thrombophlebitis, cellulitis, osteomyelitis, etc.[33] Serial ultrasound studies are useful following abscess formation and to guide percutaneous drainage.[20] CRP and ESR levels are elevated but muscle enzyme levels such as creatine kinase and aldolase are generally normal.[1]

CHAPTER 2
Introduction to Describing Pediatric Musculoskeletal Infection Disease Severity

The epidemiology of pediatric musculoskeletal infection, including clinical manifestations, causative organisms, and demographics, is evolutionary in nature. There is moderate variability in the reporting of these conditions depending on the source country or geographical region. Even within a single institution, there may be substantial variability in the clinical epidemiology of this disease when chronologically separate cohorts are compared.[36] A major transformative factor has been the increasing incidence of community-acquired MRSA (Methicillin-resistant *Staphylococcus aureus*). The disease prevalence of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* (CA-MRSA) has increased significantly from 10/100,000 in the period 1988-1990 to 250/100,000 in 1993-1995.[37] There has also been a concurrent increase in incidence of CA-MRSA in patients without an identifiable risk factor (prolonged hospitalization, invasive surgical procedures, indwelling catheters, endotracheal tubes, prolonged exposure to antibiotics) between the period of 1988-1990 and 1993-1995.[37]

Several reports indicate that there is variability in the clinical manifestations of deep musculoskeletal infection caused by *S. aureus* depending on the strain of the organism. CA-MRSA may be associated with increased clinical disease severity as compared to CA-MSSA (Community-Acquired Methicillin-Sensitive *Staphylococcus aureus*), as noted by: CRP>4, ESR>40, anemia, and arthritis.[38] Furthermore, CA-MRSA appears to yield a more complicated disease course and outcome, with increased days of positive bacterial cultures; increased days until defervescence; complications, such as chronic osteomyelitis, pathologic fractures, or DVT; abscesses; need for surgery; increased days until ESR normalization; total days on antibiotics; and total length of hospitalization. [38-40]

Apart from the difference in antibiotic resistance profile, strains of MRSA may differ in the expression of virulence factors which are presumed to be associated with the development of severe complications. One of the most studied virulence factors is Panton-Valentine Leukocidin(PVL) which allows for WBC lysis and the promotion of tissue necrosis.[41] Children infected with MRSA carrying PVL have increased rates of life-threatening infections requiring ICU admission, extracorporeal membrane oxygenation for acute multisystem failure, and vasopressors for hypotension/septic shock.[41] There also appears to be a positive correlation of PVL and the occurrence of DVT, chronic osteomyelitis, fixed elbow contractures, heterotopic ossification, and distal tibial physeal arrest.[41]

Thus, due to the great breadth of clinical manifestations, there is interest in understanding and accurately characterizing the disease process of pediatric musculoskeletal infections with respect to illness severity. While several epidemiologic studies have attempted grapple with severity of illness classification, there is currently no accepted standard by which to categorize the relative degree of illness of children with deep musculoskeletal infection based upon objective clinical data.

Van den Bruel et al. performed a systematic review of the literature for clinical parameters that had high positive likelihood ratio for producing serious pediatric infectious disease, defined as: pneumonia, cellulitis, osteomyelitis, sepsis, meningitis, gastroenteritis, complicated UTI, and viral respiratory infection. The research culminated in the inclusion of 36 studies which identified reduced consciousness, convulsions, cyanosis, rapid breathing, slow capillary refill as being significantly predictive of serious cardiopulmonary disease (positive likelihood ratio > 5.0).[42] Of note, both parental concern and the instinct of an experienced physician that "something is wrong" were considered significant predictors of disease in the setting of serious pediatric infections (positive likelihood ratios of 14.40 and 23.50, respectively).[42] Thus, Van den Bruel's research reminds us that although we may focus on the identification of objective clinical parameters in assessing the possibility of severe disease, the impression by parents and clinicians may be important in the development of a disease classification model.

Caird et al. designed a study based on the work of previous authors in the identification of clinical predictors to the diagnosis of septic arthritis vs. transient synovitis. Five factors were deemed to be strongly indicative of septic arthritis of the hip: 1) fever (>38.5); 2) elevated CRP; 3) elevated ESR; 4) refusal to bear weight; 5) elevated WBC count. Children with five predictive factors had a 98% chance of having septic arthritis, those with four factors had a 93% chance, and those with three factors had an 83% chance.[43]

Saavedra-Lozano and the members of our institution, using linear regression analysis on patient data involving comparisons of disease manifestation of MRSA vs. MSSA with clinical objective parameters, identified 3 independent parameters associated with negative outcome in children with acute osteomyelitis due to MRSA vs. MSSA: 1) days to normal CRP; 2) days to normal ESR; 3) days of hospitalization.[38]

The aim of our study is to develop a reliable and reproducible scoring system for severity of illness in pediatric musculoskeletal infection. An objective method to categorize severity of illness among children with deep infections is desirable in that it would allow for proper perspective when comparing cohorts of children who are separated geographically or chronologically. Also, if children have been treated with varying protocols or guidelines, it is relevant to know whether improvements in clinical outcomes are a reflection of the treatment method or are merely a factor of the relative severity of illness. The recognition of children with the highest severity of illness might indicate a more aggressive treatment response if these children could be identified early during the course of evaluation.

In this study we will evaluate objective clinical data of children with osteomyelitis, septic arthritis, pyomyositis, and abscesses who were treated at a tertiary medical center so as to elucidate the objective clinical parameters which may be relevant to the categorization of illness severity. A secondary purpose of this study is to assess the level of agreement between experts experienced in treating pediatric musculoskeletal infections in terms of identifying objective clinical parameters most predictive of disease severity and the classification of disease severity in our patient cohort.

CHAPTER 3

Part 1 - Retrospective Analysis of Children with Musculoskeletal Infection at a Tertiary Pediatric Medical Center: Multiple Logistic Regression of Objective Parameters of Illness Severity Against Length of Stay and Professional Opinion

Background

The local epidemiology of pediatric musculoskeletal infection at Children's Medical Center of Dallas was previously reported over a 22-26 year period and identified that septic arthritis, had occurred at a rate of 18 cases per year and was more common than osteomyelitis, which had occurred at a rate of 11.7 cases per year. Recent experience from 2002-2004 suggested that deep infections of the musculoskeletal system had a higher incidence at our institution than indicated in the previous report. This new incidence was noted to be approximately 39 cases per year of septic arthritis and 71 cases per year of osteomyelitis and was accompanied by the onset and rising rate of CA-MRSA in our community. Our substantial experience in evaluating and treating these children led to an awareness of a marked variability in the clinical severity of illness which children with the same disease process, even with the same causative organism, might demonstrate. The current study is intended to identify objective parameters which might be useful in quantifying severity of illness in pediatric musculoskeletal infection.

Methods

343 children were evaluated and treated for osteomyelitis, pyomyositis, septic arthritis at Children's Medical Center in Dallas between January 2002 and December 2004. Investigational Review Board approval was obtained for retrospective review. Objective clinical parameters had been previously cited in our review of the local epidemiology of pediatric musculoskeletal infection at our institution.[36] Additional objective parameters were added based on the likelihood that they might serve as reasonable surrogates for illness severity given that their presence, or absence, might cause a reviewer to form differing opinions as to the relative illness of the child based on the specific parameter. Ultimately 21 objective parameters were selected: 1) Temperature on admission >38 degrees; 2) WBC count upon admission; 3) Positive blood cultures; 4) Febrile days on antibiotics; 5) Specific musculoskeletal infection diagnosis; 6) Contiguous infections; 7) Multifocal infections; 8) Other concurrent diagnoses (eg: SSD, leukemia); 9) Specific organism identified; 10) MRSA positive; 11) Peak C-Reactive Protein (CRP); 12) Peak Erythrocyte Sedimentation Rate (ESR); 13) Number of surgeries; 14) ICU admission; 15) Intubation; 16) DVT; 17) Severe complications (eg: compartment syndrome, toxic shock syndrome, septic pulmonary embolism, or pneumonia); 18) Length of hospital stay (LOS); 19) Hospital re-admission; 20) Days until lowest recorded follow-up lab value; 21) Duration of antibiotic treatment. The Length of Hospitalization (LOS) parameter was originally assumed to be the best surrogate of illness severity, and a multiple logistics regression analysis was implemented for the remaining parameters against the LOS. Standard coefficients were computed for each parameter to determine its relative correlation with LOS as a marker for illness severity.

Next, a multi-disciplinary expert panel, consisting of eight physicians (five orthopedic surgeons, two infectious disease specialists, and one pediatric hospitalist) experienced at treating pediatric musculoskeletal infections at a tertiary medical center, was asked to objectively evaluate each child's illness as being overall 1=mild; 2=moderate; or 3=severe. The panel was also required to independently review all 21 objective clinical parameters and rank order each parameter as to which would be most predictive of illness severity. Simple Kappa statistics were implemented to assess the level of agreement between the eight physicians in terms of the level of illness severity for each child and the relative weight of each of the 21 parameters in predicting pediatric musculoskeletal infection. In order to simplify the analysis of agreement of parameters amongst the members of the multi-disciplinary expert panel (an agreement score would require perfect agreement in parameter ranking and would not allow for near misses), the parameters were further sub-divided to 3 sub-groups of 7 parameters each, and the level of agreement was measured according to the parameters listed as top 7, middle 7, and bottom 7. Finally, a multiple logistic regression analysis was performed for each parameter against average disease severity score as determined by the expert panel. A backwards elimination method was used to discard variables not significantly correlated with average illness severity. A Spearman rho correlation was run to reduce the effect of outliers.

Results

I. Disease Severity as a Factor of Length of Stay

After performing multiple linear regression of the objective clinical parameters against length of stay (LOS), six variables were noted to have a statistically significant relationship with LOS ($p<0.001$) and a correlation coefficient (R^2) of 0.70, including: 1) febrile days on antibiotics; 2) antibiotic treatment duration; 3) number of surgical procedures; 4) days until lowest recorded laboratory values; 5) contiguous infections; 6) and multi-focal infections (**see Table 1**).

The regression analysis was then repeated using just the top four variables resulting in the same R^2 of 0.70 and the following standardized coefficients: Febrile days on antibiotic (0.35); antibiotic treatment duration (0.31); number of surgeries (0.28), and days until lowest recorded laboratory value (0.24). All were highly statistically significant ($p<0.0001$) (**see Table 2**).

II. Professional Ranking of Disease Severity Parameters

The average rank order of each objective clinical parameter is listed in **Table 3**. The simple kappa statistic was performed on the rankings as 21 independent entities and resulted in a kappa score of 0.08 (where 0.0 equals random ranking and 1.0 equals perfect ranking). The score of 0.08 is virtually similar to a random assignment of ranks. As noted above, a score of 1.0 requires perfect matching and no allowance for near misses. When the parameters were grouped into 3 groups of seven with upper seven (no. 1-7), middle seven (no. 8-14) and

lower seven (no. 15-21) and then re-assessed with a kappa statistic, this resulted in an improved kappa statistic score of 0.38.

III. Disease Severity Assessment

For the severity of illness determination of 1=mild, 2=moderate, and 3=severe, the expert panel had a simple kappa score of 0.34, which is considered to be poor agreement. Of the 343 children that were reviewed by the eight reviewers, a mild score was assigned 1460 times, a moderate score was assigned 1656 times, and a severe score was assigned 1368 times for an average severity of illness score of 1.63 for this population.

IV. Disease Severity as a Factor of Expert Opinion

Multiple logistic regression comparing the parameters against the average disease severity score assigned by the eight reviewers produced seven variables that have a correlation coefficient at or above 0.5, including: 1) Length of stay (LOS); 2) Number of surgeries; 3) Total febrile days on antibiotics; 4) contiguous infections; 5) Severe complications (pneumonia, SPE, toxic shock, compartment syndrome); 6) Peak ESR; 7) ICU admission (**see Table 4**). **Table 4** presents the Spearman Rho value (the correlation coefficient produced while minimizing the effect of outliers) of the seven parameters as well as their corresponding ranking assigned by the expert review panel.

Conclusions from Part 1

At the outset of this portion of our study, we were optimistic for agreement between experienced professional reviewers of our database in regards to the stratification of illness severity in pediatric musculoskeletal infections. However, based on the kappa statistics that were produced, it is clear that not only is there poor agreement between the subjective assignment of mild, moderate, severe for disease severity amongst experts, but even more fundamentally, the experts failed to come to a consensus on which objective clinical parameters would weigh most heavily in their assessment of illness severity. Presumably, the rank order of the clinical parameters would most likely influence their severity of illness assignments.

Unfortunately, there is not one perfect objective clinical parameter that is most appropriate as a surrogate for disease severity. We chose length of stay originally since logically a child who has a longer hospital course would be assumed to have a more severe disease process. However, numerous other factors can affect length of hospital stay which may be irrelevant to severity of illness, including home health placements, efficiency of the electronic medical record, timeliness of care delivery, and individualized decision making of various care providers in an academic tertiary pediatric medical center. Therefore, to counteract this issue, we performed a linear regression of clinical parameters against professional opinion instead of length of hospital stay as a predictor of disease severity. It was interesting to note that the relative weight of LOS of 0.68 was the highest of the professional opinion regression,

despite the average reviewer rank of only 8.9 for the LOS parameter. This finding emphasizes the immense challenge involved in synthesizing an objective scoring system for a disease process as varied as pediatric musculoskeletal infection not only in clinical manifestations but also expert opinion on the analysis of pertinent objective clinical data.

Surprisingly, some parameters which appeared to be relatively important to the reviewers (**see Table 3**), did not weigh heavily in the correlation against average disease severity rankings (eg. intubation and DVT), whereas other parameters which appeared to be less important to the reviewers, rose to the top of the regression (eg. ESR and duration of antibiotic treatment) (**see Table 4**). However, this is partially explained by the low rate of occurrence of these phenomena in this subset of children.

The limited amount of agreement between professionals underscores the need for a consensus on severity of illness categorization for pediatric musculoskeletal infections. In the current healthcare model, , medical decisions regarding imaging, laboratory tests, surgery, and discharge planning for children with musculoskeletal infection are largely dependent upon the medical professional's perception of objective clinical data. Therefore, we cannot neglect the importance of professional opinion in attempting to quantify severity of illness.

Part 1 of this study was inherently limited by the retrospective methodology and by the fact that the study period was during a period at our institution in which care for children with musculoskeletal infection was not highly standardized. Therefore, it is difficult to draw firm conclusions that allow reliable assessment of severity of illness on the basis of this study. However, it is possible to consider that the parameters identified in part 1 may have some relationship with illness severity which merits inclusion in the methodology for the next part of this research. The conclusions of part 1 of our study are: 1) With LOS as a surrogate for disease severity, there is positive correlation with duration of antibiotic treatment, number of febrile days on antibiotics, days until normalization of laboratory indices, and number of surgeries; 2) according to professional opinion (as diverse as it may be), disease severity is positively correlated with LOS, number of surgeries, febrile days on antibiotics, severe complications (pneumonia, SPE, toxic shock, compartment syndrome), contiguous infections, peak ESR, ICU admission, peak CRP, bacteremia, and multi-focal infections.

CHAPTER 4
Part 2 - Analysis of Children with Musculoskeletal Infection at a Tertiary Pediatric Medical Center: Cohort of Children Treated According to Evidence-Based Clinical Practice Guidelines by a Multi-Disciplinary Team

Background

In 2005 a multi-disciplinary committee was assembled at Children's Medical Center of Dallas to develop clinical practice guidelines for the evaluation and treatment of pediatric osteomyelitis, septic arthritis, pyomyositis, and deep abscesses. An extensive level of evidence review of pediatric musculoskeletal infection literature was accomplished, including 1600 articles published from 1994 to 2007. From this literature review, the guidelines were graded and found to be well aligned with the current evidence. The guidelines were then implemented by a multi-disciplinary service who met daily on the hospital wards to review care for the children to ensure that the guidelines were being followed.

Methods

Between January 1, 2009 and December 31, 2009, we consecutively studied 137 children who were evaluated and treated for osteomyelitis, septic arthritis, pyomyositis, and surgically drained abscesses. These children were treated by the multi-disciplinary team according to evidence based clinical practice guidelines (**see Figures 1-5**). The multi-disciplinary team included: orthopaedic surgery, pediatrics, infectious disease, nursing, and social work. Investigational Review Board (IRB) approval was obtained for this study. The following objective clinical parameters were deemed to be predictive of severity of illness for pediatric musculoskeletal infections: 1) Fever (temperature above 38.0° C) upon admission; 2) white blood cell count (WBC) upon admission; 3) positive blood cultures (bacteremia); 4) febrile days on antibiotics; 5) contiguous infection; 6) multi-focal infection; 7) MRSA culture positive; 8) Peak C reactive protein (CRP) level in mg/dL; 9) Peak erythrocyte sedimentation rate (ESR) in mm/hr; 10) number of surgical procedures; 11) intensive care unit (ICU) admission; 12) intubation; 13) identification of deep venous thrombosis (DVT); 14) identification of specific complications, such as compartment syndrome, toxic shock syndrome, septic pulmonary embolism (SPE) or pneumonia; 15) length of hospital stay (LOS); 16) re-admission after discharge; 17) days until laboratory value normalization; and 18) duration of antibiotic treatment. In addition, for child, the specific musculoskeletal infection diagnosis (eg: osteomyelitis of distal phalanx of left fourth toe with abscess) was recorded to help our expert panel of reviewers understand the clinical context of the specific type of infection.

A panel of eight physicians (five orthopedic surgeons, two infectious disease specialists, and one pediatric hospitalist), who are experienced in the treatment and management of pediatric musculoskeletal infection, was again assembled at our institution. Similar to part 1, each expert on the panel was asked to independently review the list of objective clinical parameters and rank-order each parameter based on which parameters would most likely

predict clinical severity. They were also permitted to review the findings of part one of our study so as to gain better perspective of the intent of this research. Kappa statistic was used to assess the level of agreement of reviewers on the panel and identify any outliers present. The physician panel was then asked to review each objective clinical parameter for each child and to rate each child's disease severity based on the following scale: 1=mild, 2=moderate, 3=severe. We then grouped the moderate and severe categories of patients together and compared them against the mild patients in order to have sufficient numbers in both groups. A binary logistic regression and a fisher's exact test were implemented to identify parameters with significant differences when comparing patients with mild rating with those with a rating of mild or severe.

Results

I. Study Population and Data Collected

Of the 137 children retrospectively reviewed, 53 children were diagnosed with osteomyelitis, 30 children were diagnosed with septic arthritis, five children were diagnosed with pyomyositis, and 49 children were diagnosed with abscesses. To ensure consistency of care, children were admitted to our multi-disciplinary service and treated according to the evidence-based clinical practice guidelines which were established at our institution (**see Figures 1-4**). **Tables 5 and 6** summarize the cohort results in terms of the presence and absence of each non-continuous objective clinical parameter and mean, minimum, maximum, and standard deviation for each continuous objective clinical parameter included in our study.

II. Professional Ranking of Disease Severity Parameters

The rankings of each of the 19 objective clinical parameters was obtained and studied with a simple Kappa statistic to identify the level of agreement amongst the eight members of our expert panel. However, an outlier analysis produced a reviewer whose ranking deviated substantially from the remaining seven. Therefore, this reviewer's proposed ranking was excluded from subsequent analysis. Similarly to our previous study, because the Kappa statistic does not allow for near misses, the ranking system for the parameters was again grouped into 3 groups. Kappa analysis resulted in a negative Kappa score for four parameters: febrile days on antibiotics, peak CRP, days until laboratory normalization, and length of antibiotic treatment. The above four parameters were thereby excluded from the Kappa analysis. The final statistic with the remaining 15 parameters grouped into three groups (top five, middle five, bottom five), with exclusion of the outlier, produced a Kappa score of 0.63, indicating substantial agreement between the expert panel members.

III. Disease Severity Assessment

The disease severity scores were compiled from each reviewer (excluding the outlier) and the mode, instead of the mean used in the previous study, was used as a marker for disease

severity. A mild score was assigned for 100 patients; a moderate score was assigned for 30 patients; a severe score was assigned for 7 patients. Due to the limitations in numbers for children in the severe category, the numbers in the moderate and severe categories were combined together for subsequent statistical analysis.

IV. Disease Severity as a Factor of Expert Opinion

Binary logistic regression analysis was conducted to determine the odds ratio and the 95% confidence intervals for each of the ten continuous objective clinical parameters when comparing the mild and moderate/severe groups of patients (**see Table 7**). Three parameters were identified to be significantly associated with a moderate or severe disease rating by our physician panel: 1) number of surgeries ($p<0.05$); 2) total length of hospitalization ($p<0.01$); 3) total length of antibiotic treatment ($p<0.01$). The remaining five variables were studied with Fisher's exact test (**see Table 8**). Three parameters were identified and found to be significantly associated with moderate/severe disease: 1) ICU admission ($p<0.05$); 2) Hospital readmission ($p<0.0001$); 3) Severe complications ($p<0.0001$).

Conclusions from Part 2

The validity of this portion of the study has been improved over part 1. The children in part 2 were cared for according to evidence-based clinical guidelines by a multi-disciplinary team. Therefore, the clinical course of the 137 children consecutively studied is a reflection of uniform care and the differences between children are presumably due to the underlying disease process and as opposed to discrepancies in plans of care.

Furthermore, the Kappa statistic of 0.63 was substantially improved from 0.38 in part 1 of our study with the exclusion of the opinions of an outlier. This suggests an improved consensus of opinion among members of our panel and lends increased credibility to the ability of the panel to distinguish between the parameters within their decision algorithms while assessing individual patients for severity of illness.[2intro8]

Both the binary logistic regression analysis for continuous objective clinical parameters and the Fisher's exact test for non-continuous objective clinical parameters yielded six significant parameters positively correlated to a moderate/severe disease rating, including: 1) number of surgeries ($p<0.05$); 2) total length of hospitalization ($p<0.01$); 3) total length of antibiotic treatment ($p<0.01$); 4) ICU admission ($p<0.05$); 5) Hospital readmission ($p<0.0001$); 6) Severe complications ($p<0.0001$).

Taking into account the findings of the first two parts of our study, there were four objective parameters that were noted to be significantly associated with increased severity of illness in children with musculoskeletal infection: 1) Length of hospitalization; 2) Number of surgeries; 3) Severe complications (eg: compartment syndrome, toxic shock syndrome, septic pulmonary embolism, or pneumonia); and 4) ICU admission.
These findings are the result of an exhaustive attempt to identify objective clinical parameters

that are most predictive of severity of illness for pediatric musculoskeletal infection. This endeavor sheds light on one potential parameter that has the greatest likelihood to develop an objective scoring system for deep infections, which is number of surgeries. Among the remaining parameters, two are clinically rare, ICU admission and the presence of severe complications. Both of these parameters will clearly establish a high severity of illness as soon as they occur. Length of hospitalization remains challenging to use in a scoring model because it is an end state effect of the disease process and would not be known or knowable at the point of care in which the treating team would gain the greatest benefit.

One major limitation of parts 1 and 2 of this research is the inclusion of more than one subset of disease in the regression analyses. It became clear that the professional reviewers on the panel had a difficult time shifting attention between osteomyelitis, septic arthritis, pyomyositis, and abscess categories. In order to reduce the number of variables impacting severity of illness classification it would be beneficial to only deal with one disease category.

CHAPTER 5
Part 3 - Prediction of Surgical Intervention in Children with Acute Hematogenous Osteomyelitis Based on Preliminary Clinical and Laboratory Parameters

Introduction

As evidenced by parts 1 and 2 of this study, the number of surgeries correlated positively when assessed against LOS and professional opinion as surrogates for severity of illness. Furthermore, number of surgeries was identified as a significant predictor of moderate/severe disease rating as designated by our musculoskeletal disease expert panel with substantial agreement among panel members. Thus, it is logical to utilize number of surgeries as a surrogate for disease severity.

Effective treatment of children with osteomyelitis includes antibiotics and possible surgery. The decision for surgery requires the interpretation of clinical, laboratory, and radiographic evidence during an initial evaluation. Although evidence of an abscess formation in and around bone during advanced imaging is commonly cited as an indication for surgery, additional indications include consistent failure of improvement of clinical states and laboratory markers while on initial antibiotic therapy, increased febrile days on antibiotics, and/or the development of sepsis.

The purpose of this study is to determine objective clinical parameters early in the treatment of osteomyelitis in a pediatric population which are predictive for the need for further surgery. Our hypothesis is that there are clinical manifestations and laboratory values which are predictive for the need for one or multiple surgeries in pediatric acute hematogenous osteomyelitis.

Methods

In part 3 of the study, we further refined our objective clinical parameters to only include those which are present early in the course of treatment. This was done in order to establish a scoring system at presentation which might be capable of predicting the need for surgery as a surrogate for disease severity. Children identified as having higher severity of illness scores would potentially benefit from more aggressive intervention as opposed to those who are found to have lower severity of illness scores, who could be treated more conservatively.

As it was recognized that dealing with more than one sub-type of infection was a major limitation in the study designs of parts 1 and 2, we chose to deal exclusively with the osteomyelitis subset. Because this subset is responsible for the largest number of hospital bed days per year among the various sub-types of musculoskeletal infection, focusing on this group of children would potentially have the greatest impact on a future care model

Retrospective review was undertaken of 57 children with osteomyelitis treated at Children's Medical Center in Dallas between January 2009 to December 2009 following approval by the

institutional review board. The children were uniformly treated by a multi-disciplinary team and uniformly treated according to established evidence-based clinical practice guidelines. Surgical intervention was deemed necessary if a patient had evidence of intraosseous, sub-periosteal, or extra-periosteal abscess on magnetic resonance imaging (MRI) obtained by protocol within 24 hours of admission. Additional surgery was performed if a child did not show appropriate clinical or laboratory improvement within 96 hours of initial surgery.

Objective clinical parameters used in analysis included the following: 1) age; 2) gender; 3) race; 4) weight; 5) temperature on admission; 6) admission vital signs (systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate); 7) weight bearing status; 8) presence of swollen extremity; 9) admission laboratory values (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin, hematocrit, white blood cell count (WBC), and WBC with differentiation (eosinophils, basophils, monocytes, neutrophils)); 10) culture results (blood and direct tissue specimen, when available); 11) MRI findings (measurement of length, width, and depth of osseous inflammation and abscesses, if identified; finding of an adjacent joint effusion); 12) laboratory trends [CRP and ESR following initial treatment (48 hours and 96 hours post surgery or admission antibiotic admission)]; 13) febrile days (temperature > 38.0°C) while on antibiotics; 14) confirmed presence of contiguous infection (septic arthritis, pyomyositis, or abscess); 15) confirmed multi-focal infection; 16) type of antibiotic; 17) use of surgical drains; 18) drain type; 19) amount of drain output; 20) number of days of drain use; 21) intensive care unit (ICU) admission, and 22) use of inotropic support in the ICU.

Uni-variate analysis was performed with ordinal logistic regression, Chi-square, Fisher extact, and Wilcoxon rank sum and two value tests. Multi-variate logistic regression was used to identify independent predictors of surgical intervention. For comparative analysis, children were divided into groups depending on whether they had had 0, 1, or more than 1 surgical procedure during their treatment course.

Results

57 children with osteomyelitis between January 2009 and December 2009 were included in this study. The average age of patients was 6.8 years. There were 32 males and 25 females. According to blood and tissue culture results (**see Figure 6**), 18 children (32%) were culture positive for Methicillin-sensitive *Staphylococcus aureus* (MSSA), 16 children (28%) were culture positive for Methicillin-resistant *Staphylococcus aureus* (MRSA), 11 children (19%) were culture positive for a variety of other organisms, and 12 (21%) had negative culture results.

Sixteen children (28%) did not require surgery and were successfully treated with antibiotic therapy alone while 41 children (72%) required at least one surgery. Among children requiring surgical intervention for successful treatment, 29 children (71%) required one surgery and 12 children (29%) required two or more surgeries for resolution of infection (**see Table 9**).

I. Comparing children without surgery to those treated with surgery

Uni-variate analysis failed to show significant differences between children without surgery and those with surgery for the following objective clinical parameters: age, gender, race, weight, admission temperature, systolic or diastolic pressure, heart rate, WBC, differential cell count, hematocrit, blood or tissue culture results, and initial weight bearing status. Significant differences, however, were noted for the following variables: 1) presence of a swollen extremity, 2) admission CRP and ESR values, 3) admission hemoglobin, and 4) triage respiratory rate (**see Table 10**).

Using multiple logistic regression analysis, we found three variables which are significant predictors for requiring at least one intervention for treatment of osteomyelitis: 1) presence of a swollen extremity (p=0.002), 2) initial CRP value greater than 9.9 mg/dL (p=0.02), and respiratory rate greater than 27 at admission (p=0.02).

Table 11 shows the percentage of patients who had one surgery and more than one surgery based on the presence of the above predictive factors (presence of a swollen extremity, CRP > 9.9 mg/dL, respiratory rate > 27). 9 out of 57 patients had none of the three predictive factors on admission; of these 9 patients, 4 patients (44%) had one surgery during their treatment of osteomyelitis, and none had more than one surgery. 18 out of 57 patients had one of the three predictive factors; of these 18 patients, 9 (50%) needed one surgery, and only one patient (5%) needed more than one surgery. 25 out of 57 patients had two of three predictive factors; of these 25, 23 patients (92%) needed at least one surgery, and 7 patients (28%) needed more than one surgery. Finally, 5 out of 57 patients had all three predictive factors; of these 5, all required at least one surgery, and 4 patients (80%) needed more than one surgery.

II. Comparing children with one surgery to those treated with two or more surgeries

Univariate analysis failed to show significant differences between children requiring one surgery and those requiring more than one surgery for treatment of osteomyelitis with respect to the following variables: demographics, admission vitals, laboratory values other than CRP, MRI findings, contiguous or multi-focal infection, culture results, drain use, type, or duration, intubation, or pressor support. Significant differences, however, did identify the following parameters being significantly correlated with the need for two or more surgeries: 1) ICU admission; 2) febrile days on antibiotics; and 3) CRP values on admission, 4) 48 hours post initial surgery, and 5) 96 hours post initial.

Multiple logistic regression analysis showed that in children who have one surgery, the factors most predictive of multiple surgeries include: 1) febrile days on antibiotics; 2) CRP values at admission, 3) at 48 hours, 4) and 96 hours post-surgery (**see Table 12**). **Table 13** shows the percentage of patients who had one surgery and more than one surgery, respectively, based on the presence of these predictive factors.

Conclusions from Part 3

There has been an emergence of community acquired MRSA, which has impacted the processes of care for deep musculoskeletal infection at our institution. This has been associated with an increased incidence of challenging cases of osteomyelitis, as reflected by more contiguous abscess formation and a higher number of surgeries necessary for treatment.

To this date, there have not been any published guidelines for the indications of surgery in the treatment of acute pediatric osteomyelitis. The Finnish study group has suggested that the majority of children with osteomyelitis may be successfully treated with 20 days of intravenous antibiotics and without major surgery. However, they have do not report CA MRSA within their community. The recommendations of the Finnish group would most likely not be beneficial to our study population given the increased virulence and invasiveness of the organism.

One of the limitations of the study is its retrospective design and the small amount of pediatric cases for review. Selection bias was avoided by the inclusion of all children within a series of consecutive admissions from January 2009 to December 2009.

Although no guidelines have been established regarding the management of children suffering from acute hematogenous osteomyelitis, our institution has developed evidence-based clinical practice guidelines graded with a 14 year level of evidence review pertaining to pediatric musculoskeletal infections. Patients were followed routinely by a multi-disciplinary team which met daily for conferences and decisions regarding level of treatment. This ensured greater uniformity of care among our patient cohort. By our protocol (**see Figure 1**) children suspected of having a deep musculoskeletal infection are to have an MRI with or without contrast to be completed within 24 hours of admission. The MRI is to be reviewed by the orthopedic attending physician and radiology attending physician for the presence of intra-osseous, sub-periosteal, or exta-periosteal abscesses. If an abscess is detected, routine surgical drainage of the abscess along with irrigation and debridement of infected bone is warranted. Children who do not demonstrate abscess formation and are not septic can be managed conservatively with intravenous antibiotic therapy along with close serial monitoring (every 48 hours) for laboratory and clinical improvement without surgery. Additional indications for surgery is failure of improvement of labs or clinical states within 96 hours of surgery or persistent fevers while on antibiotic therapy. Additional surgery is to be performed without repeating MRI.
Given our concerns for the common occurrence of contiguous abscesses on initial MRI, there is a tendency toward early surgical intervention even if the abscess appears small (<1 cm). However, children with small abscesses may improve and resolve their infections with antibiotic treatments alone.

Among the nine children who had zero or only one risk factor, four children underwent initial surgical debridement and none required required subsequent surgical debridements. A more

detailed review of the four cases revealed small abscesses: one child's abscess measured 2 cm, and the rest measured less than 1 cm. In retrospect, it is possible that children with zero or only one risk factor could have resolved their infection with intravenous antibiotic treatment alone without the need for surgery, particularly in the presence of small abscesses (<1cm).

12 children required more than one surgery during their hospitalization. On average, these children had their second surgery an average of 6.5 days after the index procedure. A more detailed review of the cases revealed that the need for more than one surgery during admission was predicted by four parameters: 1) four or more days on antibiotics; 2) an admission CRP level greater than 19.8 mg/dL; 3) CRP level at 48 hours after surgery greater than 21.5 mg/dL; and a CRP level at 96 hours after surgery greater than 15.3 mg/dL. The following findings lends credibility to the notion that CRP level is very influential in the surgical decision-making process during the acute inflammatory phase of pediatric hematogenous osteomyelitis. Therefore, CRP at admission is not only predictive of one surgery but also of multiple future surgeries during the course of hospitalization.

It is important to note that the objective clinical parameter, number of surgeries, has been identified as a parameter which positively correlated significantly with length of stay (LOS) from Part I and moderate/severe disease severity rating as determined by an expert panel from Part II. These previous studies lend credibility for number of surgeries as a surrogate for disease severity in children with musculoskeletal infections.

Our study was able to identify important clinical parameters which are predictive of the need for one or more future surgeries in children with osteomyelitis. These parameters can help guide us towards the need for surgery when overt indications for surgery, such as large abscesses on imaging, are otherwise absent or alternatively when MRI is unavailable for use. The information will also be useful guiding the decision for early discharge in a patient whose parameter measurements classify him/her as a low-risk for future surgeries, allowing for outpatient antibiotic treatment. Our study also suggests that the parameters which predict surgery may indirectly be used as an objective scoring system for severity of illness for pediatric osteomyelitis. As such, we have proposed a simplified 10 point scoring system utilizing the objective clinical parameters of: 1) initial CRP value; 2) initial ESR; 3) initial Hemoglobin; and 4) triage respiratory rate (see table 14). This severity of illness scoring system will need to be validated by prospective clinical outcomes research to verify that children with the highest severity of illness scores indeed require the greatest amount of resources for care, have the highest complication rate, and have the poorest clinical outcomes. Internally checking our scoring system, we have assessed severity of illness score against culture identification of MRSA, MSSA, other organism, or no growth; and the occurrence of contiguous infections (see tables 15-16). In each of these, there appears to be a positive correlation which confirms that we are on the right track with this initial, simplified scoring system for severity of illness in children with osteomyelitis.

Table 1: Disease severity regression evaluating objective parameters against length of hospitalization.

Disease Severity Parameter	Coefficient	p-value
Total febrile days on antibiotics	.30	<0.0001
Duration of antibiotic treatment	.28	<0.0001
Number of Surgeries	.24	<0.001
Lowest laboratory value (days)	.22	<0.001
Contiguous infections	.15	<0.001
Multi-focal infections	.14	<0.001
WBC at admission	-.06	0.07

Table 2: Disease severity regression evaluating four isolated parameters against length of hospitalization.

Disease Severity Parameter	Coefficient	P-value
Duration of antibiotic treatment	.35	<0.0001
Total febrile days on antibiotic	.31	<0.0001
Lab Normalization days	.28	<0.0001
Number of Surgeries	.24	<0.0001

Table 3: Professional reviewer ranking of the relative importance of the objective parameter in influencing their perception of disease severity for individual children.

Rank	Parameter	Average Rank	Range
1	Intubation	1.8	1-3
2	ICU admission	2.1	1-3
3	Other complication (SPE, pneumonia, toxic shock)	2.1	1-3
4	Surgical procedures	5.8	5-7
5	Deep venous thrombosis	6	4-10
6	Multi-focal infection	7	4-13
7	Bacteremia	8.5	4-12
8	Total LOS	8.9	4-17
9	Febrile days on antibiotics	9.8	5-16
10	Re-admission	10.4	7-16
11	Specific musculoskeletal infection diagnosis	13.1	6-17
12	Contiguous infections	13.4	8-18
13	MRSA positive	14	10-20
14	Fever on admission	14.1	9-19
15	Peak CRP	14.5	7-20
16	Specific organism cultured	15.1	12-18
17	WBC on admission	15.6	9-21
18	Length of antibiotic treatment	16.4	7-21
19	Days until lowest laboratory value	16.6	10-20
20	Other concurrent diagnosis	17.3	8-21
21	Peak ESR	18.6	15-21

Table 4. Disease severity regression evaluating objective parameters against the average disease severity ranking (1=mild; 2=moderate; and 3=severe) of 343 children.

Spearman rho	Logistic regression	p-value	Reviewer Rank	Multiple regression	p-value
.68	LOS	0.0114	8	LOS	0.0021
.66	Surgeries	<0.0001	4	Surgeries	<0.0001
.60	Febrile days		9	Febrile days	0.0018
.58	Complications	<0.0001	3	Complications	<0.0001
.57	Contiguous infect.	<0.0001	12	Contiguous infect.	<0.0001
.53	Peak ESR	0.0006	21	Peak ESR	0.0003
.50	ICU admission	<0.0001	2	ICU admission	
.49	Peak CRP	0.0002	15	Peak CRP	0.0009
.49	Bacteremia	<0.0001	7	Bacteremia	0.0005
.46	Antibiotic duration		18	Antibiotic duration	<0.0001
.27	Multi-focal infect.	0.0234	6		
	84.7% concordant			$R^2 = 0.77$	

Table 5: Noncontinuous variables recorded for 137 children with musculoskeletal infection.

Parameter	*Present*		*Absent*	
Fever on admission (T>38.0 C)	25	18.2%	112	81.8%
WBC on admission (>12 K)	64	46.7%	73	53.3%
Bacteremia	23	16.8%	114	83.2%
Contiguous infection	35	25.5%	102	74.5%
Multifocal infection	5	3.6%	114	83.2%
MRSA positive	44	32.1%	93	67.9%
Specific complications	8	5.8%	129	94.2%
Re-admission after discharge	7	5.1%	130	94.9%
ICU admission	4	2.9%	133	97.1%
Deep Venous Thrombosis	2	1.5%	135	98.5%
Intubation	2	1.5%	135	98.5%

	> 1		1		None	
Surgical procedures	25	18.2%	90	65.7%	22	16.1%

Table 6: Continuous variables as recorded for 137 children with musculoskeletal infections

Parameter	*Mean*	*Minimum*	*Maximum*	*Std. Dev.*
Total Length of hospitalization (days)	8.2	1.0	46	7.8
Peak ESR	68	3.0	145	34
Peak CRP	12	0.1	67.7	10.6
Laboratory normalization time	28.7	1.0	138	26.2
Length of antibiotic treatment	40	2.0	279	34.8
Febrile days on antibiotics	1.2	0.0	20	2.32

Table 7: Odds ratio and 95% confidence intervals from binary logistic regression on disease severity on selected parameters

Parameter	OR	95% C. I.
ContiInfectNew(1)	2.788	0.301 – 25.853
No of Surgeries (Ref: No Surgery) Greater than one Surgical procedure One Surgical procedure	23009.974* 14.325	5.721 – 9.255E7 0.039 –5311.917
Fever (Ref: No Fever)	14.237	0831 – 243.904
Total length of stay in days [a]	2.215**	1.297 – 3.781
Peak ESR Level [a]	1.001	0.966 – 1.037
Peak CRP value [a]	1.077	0.926 - 1.252
Lab normalization time ie time required to attain lowest Lab values [a]	0.984	0.942 – 1.028
LengthofdocumentedABTreatmentdays[a]	1.100**	1.028 – 1.178
TotalDocumentedFebriledaysonABs[a]	1.289	0.544 – 3.054
Bacteremia (Ref: No bacteremia)	0.389	0.018 – 8.462
R^2 = %		

Notes: a = Continuous variable; * $p<0.05$; ** $p<0.01$

Table 8: P-values for Fisher's exact test of disease severity ie moderate/severe (n = 37) or mild (n =100) on selected parameters

Parameter		Mild	Moderate / Severe	Chi - square	p-value
ICU	No	100	33	Not reported as cells are <5	0.005 * p-value for fisher's exact test
	Yes	0	4		
DVT	No	100	35	Not reported as cells are <5	0.07 * p-value for fisher's exact test
	Yes	0	2		
Intubation	No	100	35	Not reported as cells are <5	0.07 * p-value for fisher's exact test
	Yes	0	2		
Hospital Readmission	No	100	30	Not reported as cells are <5	0.000 * p-value for fisher's exact test
	Yes	0	7		
Complication	No	100	29	Not reported as cells are <5	0.000 * p-value for fisher's exact test
	Yes	0	8		

Table 9: The management of 57 children treated for acute hematogenous osteomyelitis from January 2009 to December 2009

Non-surgical management	16	28%
Surgical management		
1 surgery	29	51%
≥ 2 surgeries	12	21%
Total	57	100%

Table 10: Univariate analysis displaying objective clinical parameters at admission which significantly differed between children treated non-surgically vs. surgically for acute hematogenous osteomyelitis

	Number of Surgeries			
Parameter	0	1	2+	**(p-value)**
Swollen extremity (cases)	6 (38%)	23 (79%)	12 (100%)	0.003
Admission CRP (mg/dL)	7.5	9.9	19.8	0.005
Respiratory Rate (rpm)	21.4	27.4	28.8	0.029

Table 11: The effect of number of risk factors (swollen extremity, CRP at admission>9.9, RR at admission>27) on the surgery rate required for treatment of acute hematogenous osteomyelitis

Risk Factors	Surgery Rate	%	More than one surgery	%
0	4 of 9	44%	0 of 9	0%
1	9 of 18	50%	1 of 18	6%
2	23 of 25	92%	7 of 25	28%
3	5 of 5	100%	4 of 5	80%

Table 12: The effect of number of risk factors (febrile days on antibiotics, CRP values at admission, at 48 hours, and 96 hours post-surgery) in children with one surgery on the need for additional surgeries

Risk Factors	number of patients	1 surgery	more than 1 surgery
0	**23**	20 of 23 (87%)	3 of 23 (13%)
1	**9**	8 of 9 (89%)	1 of 9 (11%)
2	**5**	2 of 5 (40%)	3 of 5 (60%)
3	**2**	0 of 2 (0%)	2 of 2 (100%)
4	**2**	0 of 2 (0%)	2 of 2 (100%)

Table 13: Proposed scoring system in early treatment for children with acute hematogenous osteomyelitis for predicting need for future surgeries as a marker for disease severity

Objective Parameter	Score Assigned
Initial CRP	
<7	0
7-14	2
>14	4
Initial ESR	
<36	0
36-54	1
>54	2
Initial Hemoglobin	
>12	0
11.5-12	1
<11.5	2
Respiratory Rate at Admission	
<21	0
21-27	1
>27	2

Table 15. Causative organism and severity of illness score for pediatric osteomyelitis.

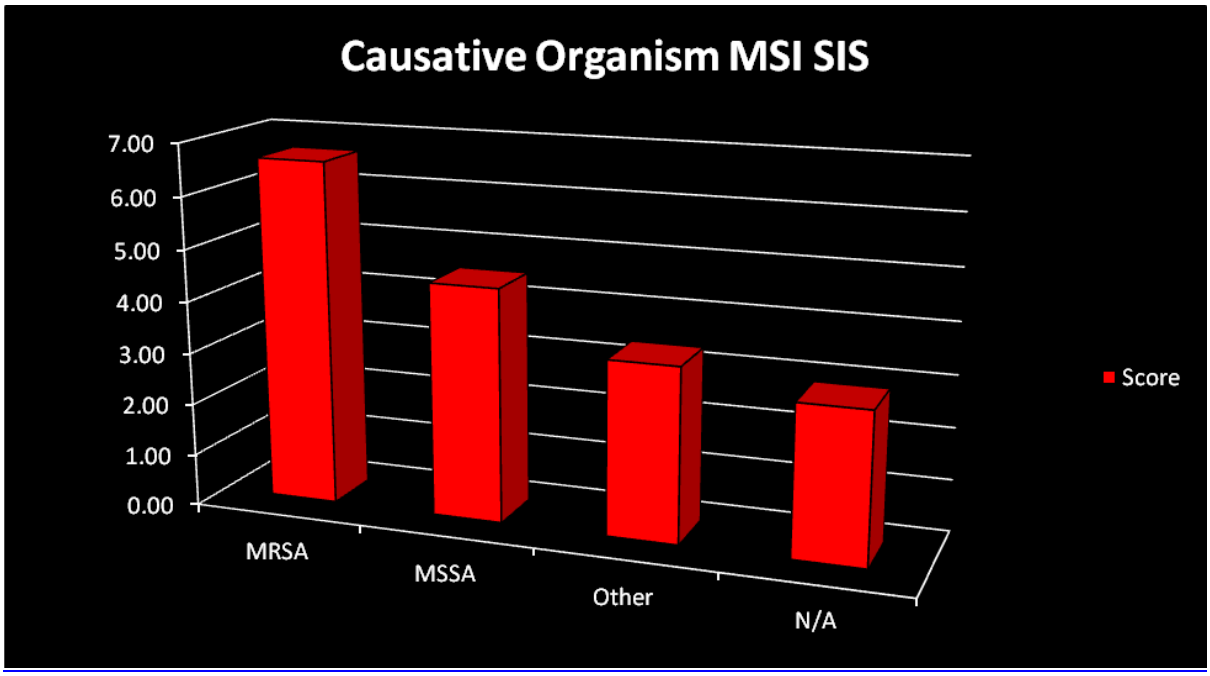


Table 16. Contiguous infections and severity of illness score for pediatric osteomyelitis.

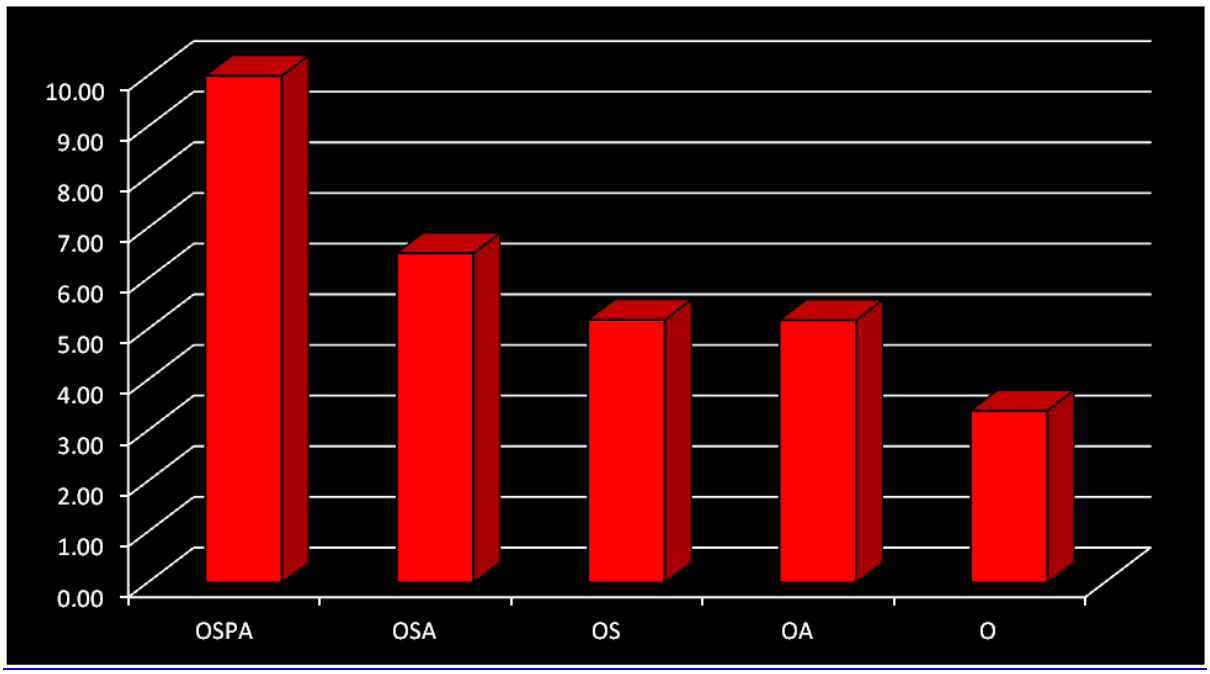


Table 14: Causative Organisms and Severity of Illness Score for Pediatric Osteomyelitis

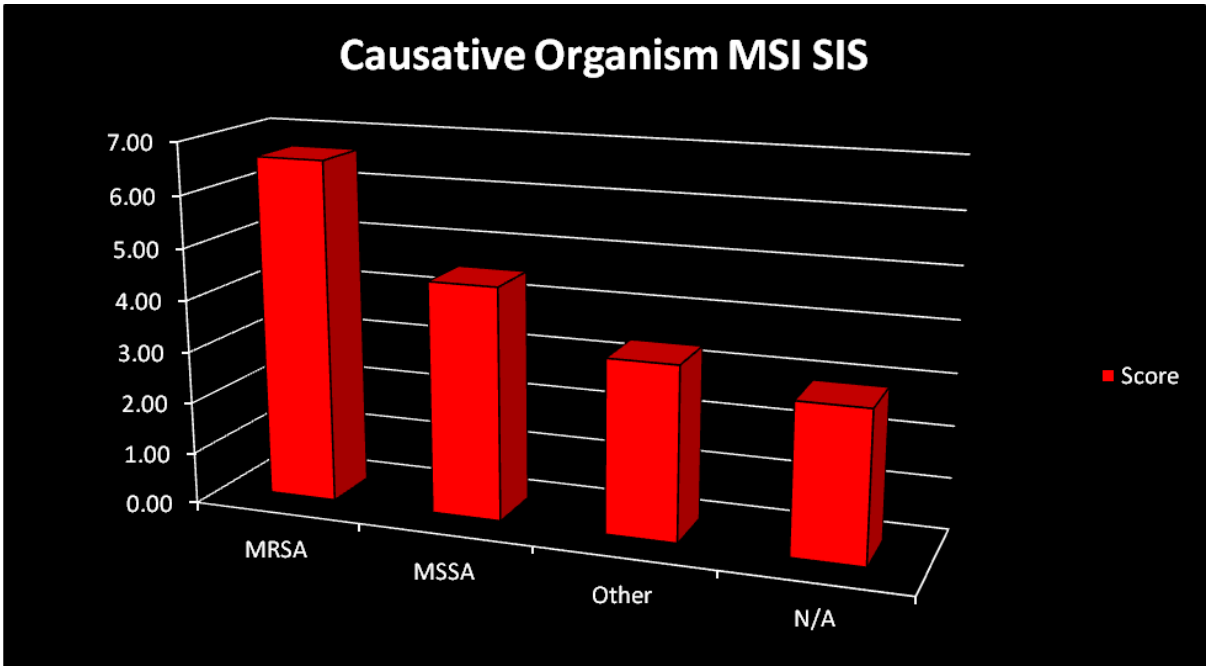


Table 15: Contiguous Infections and Severity of Illness Score for Pediatric Osteomyelitis

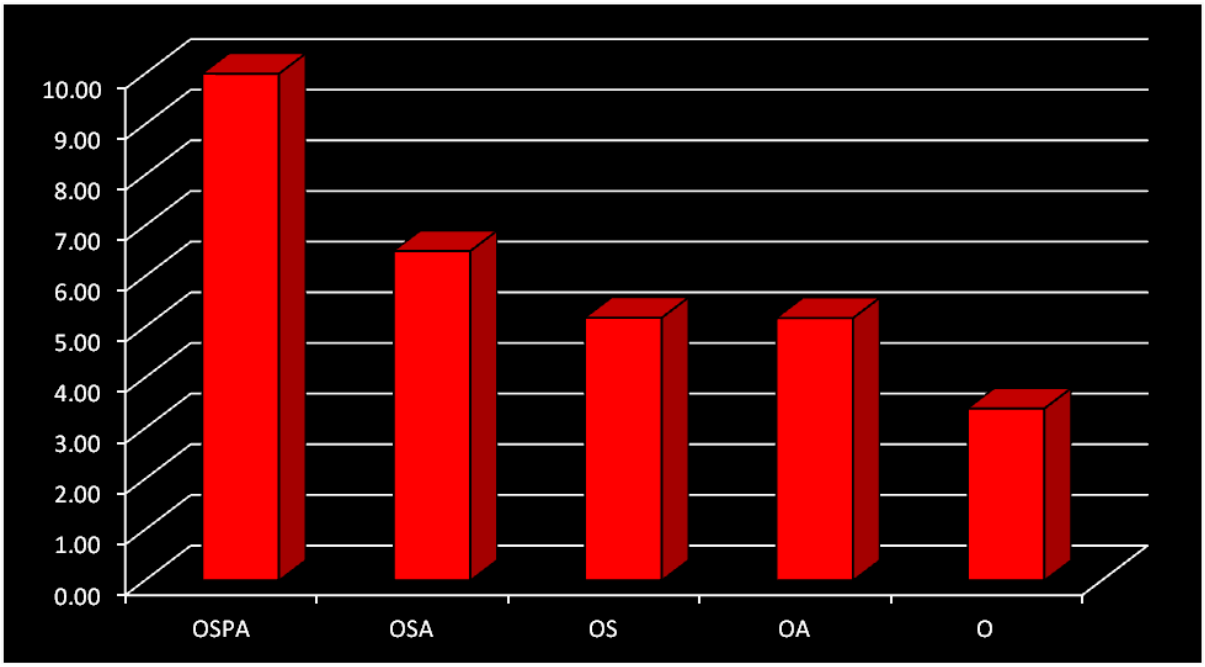
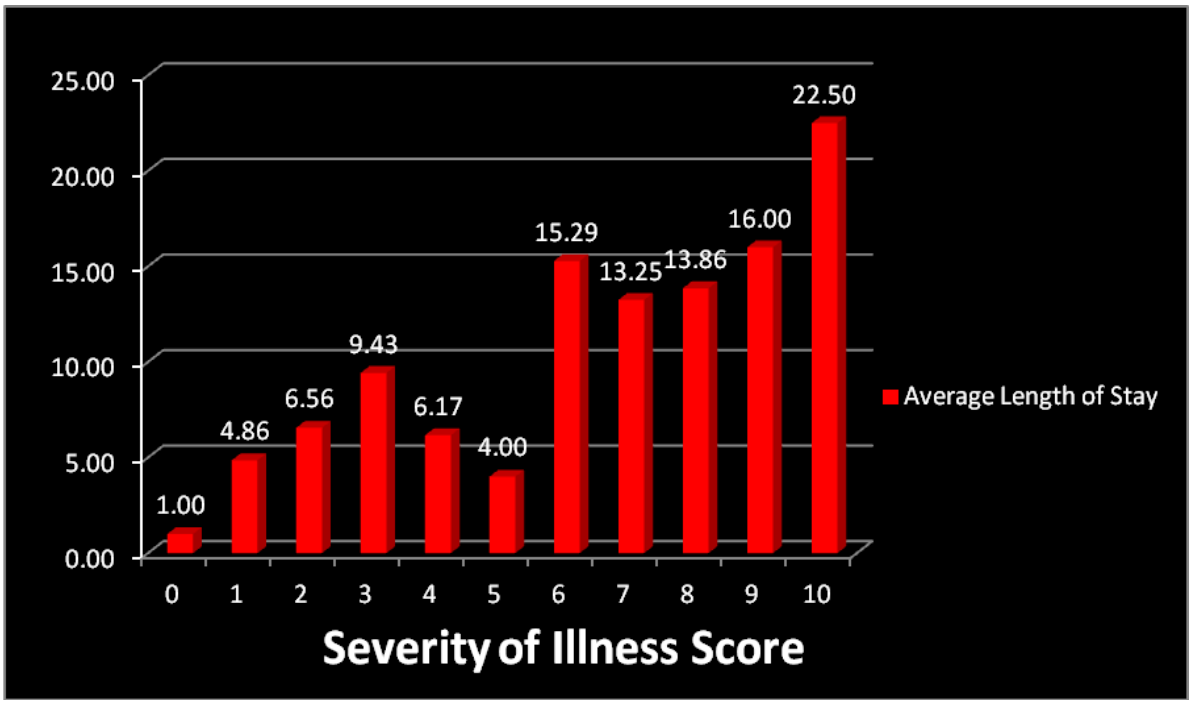


Table 16: Length of Hospitalization and Severity of Illness Score for Pediatric Osteomyelitis



Figures 1-5: Flowchart of treatment guidelines as graded by 14 year level of evidence review of medical literature on pediatric musculoskeletal infections

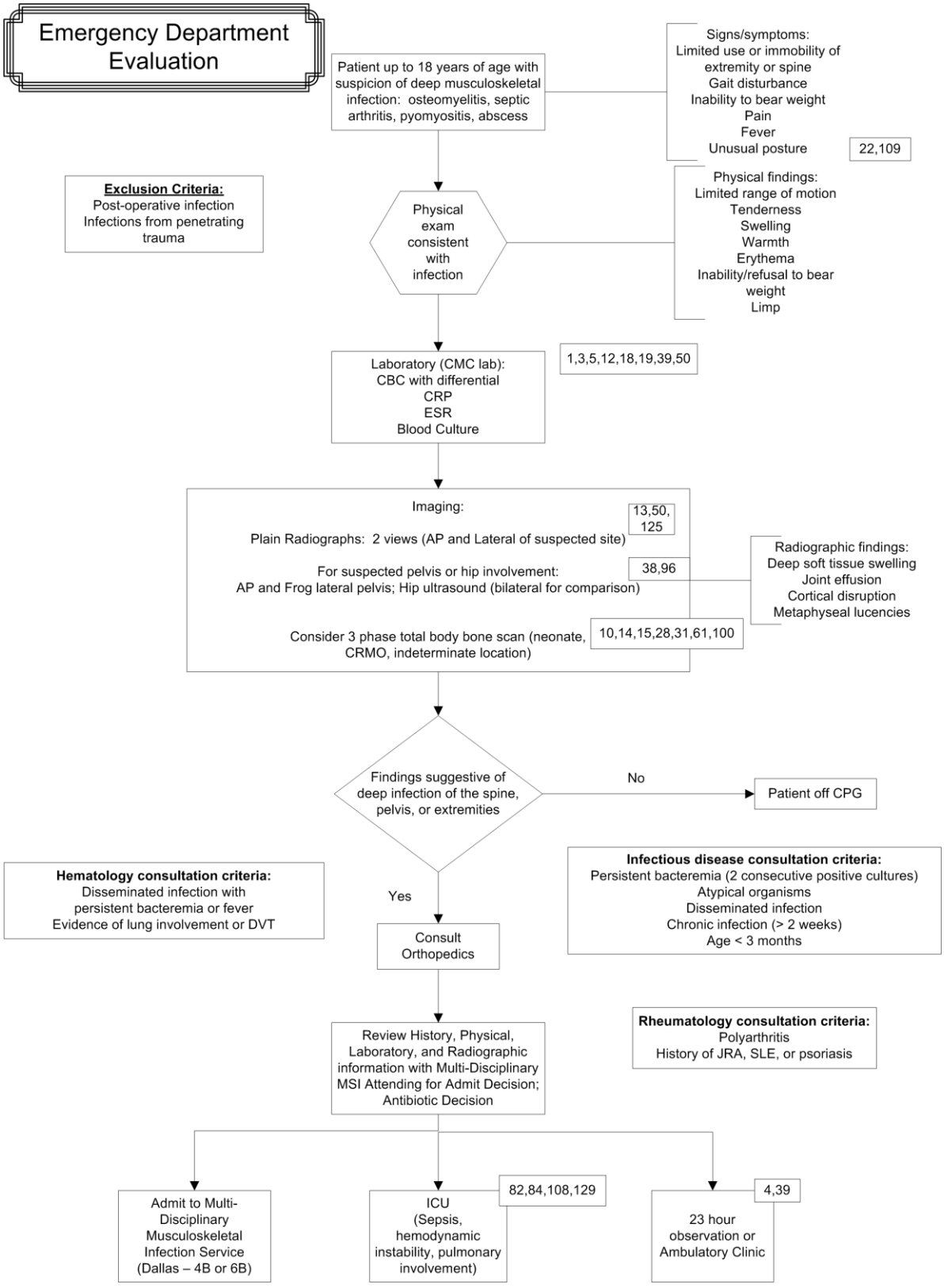


Figure 2

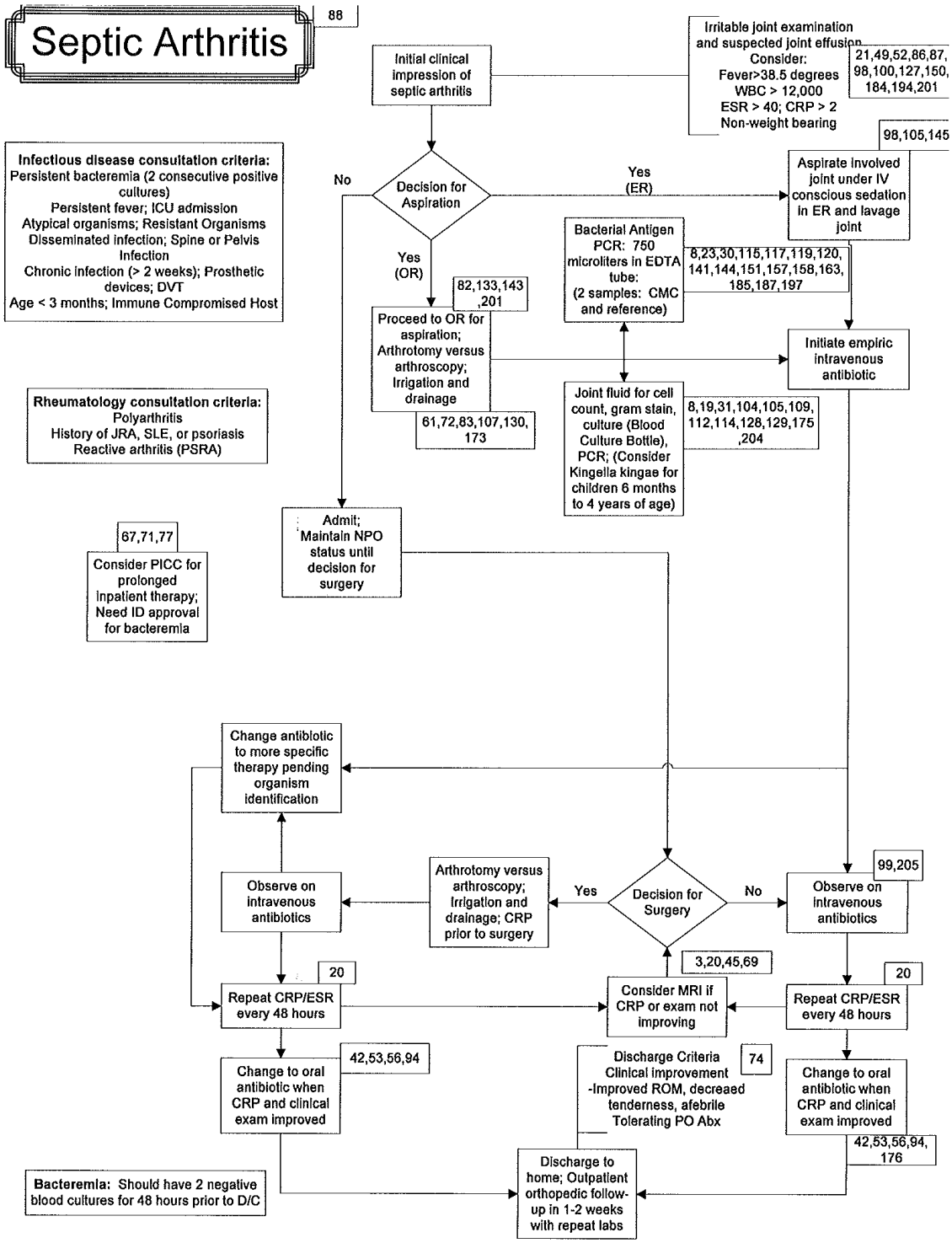

Septic Arthritis
88
Initial clinical impression of septic arthritis
Irritable joint examination and suspected joint effusion
Consider:
Fever>38.5 degrees
WBC > 12,000
ESR > 40; CRP > 2
Non-weight bearing
21,49,52,86,87,98,100,127,150,184,194,201
Infectious disease consultation criteria:
Persistent bacteremia (2 consecutive positive cultures)
Persistent fever; ICU admission
Atypical organisms; Resistant Organisms
Disseminated infection; Spine or Pelvis Infection
Chronic infection (> 2 weeks); Prosthetic devices; DVT
Age < 3 months; Immune Compromised Host
No
Decision for Aspiration
Yes (ER)
98,105,145
Aspirate involved joint under IV conscious sedation in ER and lavage joint
Yes (OR)
82,133,143,201
Proceed to OR for aspiration; Arthrotomy versus arthroscopy; Irrigation and drainage
61,72,83,107,130,173
Bacterial Antigen PCR: 750 microliters in EDTA tube:
(2 samples: CMC and reference)
8,23,30,115,117,119,120,141,144,151,157,158,163,185,187,197
Initiate empiric intravenous antibiotic
Joint fluid for cell count, gram stain, culture (Blood Culture Bottle), PCR; (Consider Kingella kingae for children 6 months to 4 years of age)
8,19,31,104,105,109,112,114,128,129,175,204
Rheumatology consultation criteria:
Polyarthritis
History of JRA, SLE, or psoriasis
Reactive arthritis (PSRA)
Admit; Maintain NPO status until decision for surgery
67,71,77
Consider PICC for prolonged inpatient therapy; Need ID approval for bacteremia
Change antibiotic to more specific therapy pending organism identification
Observe on intravenous antibiotics
Arthrotomy versus arthroscopy; Irrigation and drainage; CRP prior to surgery
Yes
Decision for Surgery
No
99,205
Observe on intravenous antibiotics
20
Repeat CRP/ESR every 48 hours
3,20,45,69
Consider MRI if CRP or exam not improving
20
Repeat CRP/ESR every 48 hours
42,53,56,94
Change to oral antibiotic when CRP and clinical exam improved
Discharge Criteria
Clinical improvement
-Improved ROM, decreased tenderness, afebrile
Tolerating PO Abx
74
Change to oral antibiotic when CRP and clinical exam improved
42,53,56,94,176
Bacteremia: Should have 2 negative blood cultures for 48 hours prior to D/C
Discharge to home; Outpatient orthopedic follow-up in 1-2 weeks with repeat labs

Figure 3

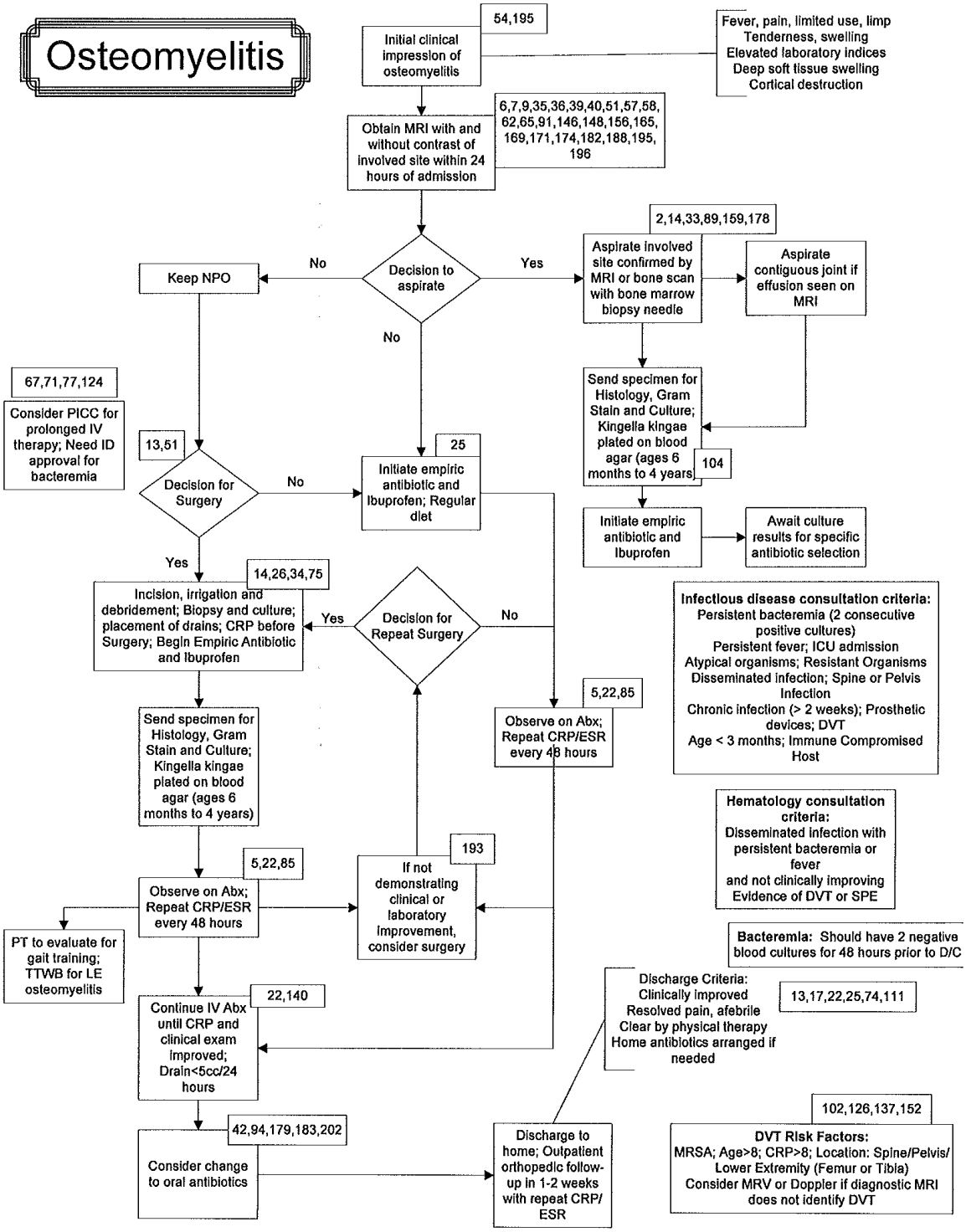

Osteomyelitis
Initial clinical impression of osteomyelitis
54,195
Fever, pain, limited use, limp
Tenderness, swelling
Elevated laboratory indices
Deep soft tissue swelling
Cortical destruction
Obtain MRI with and without contrast of involved site within 24 hours of admission
6,7,9,35,36,39,40,51,57,58, 62,65,91,146,148,156,165, 169,171,174,182,188,195, 196
Decision to aspirate
No
Yes
No
Keep NPO
2,14,33,89,159,178
Aspirate involved site confirmed by MRI or bone scan with bone marrow biopsy needle
Aspirate contiguous joint if effusion seen on MRI
Send specimen for Histology, Gram Stain and Culture; Kingella kingae plated on blood agar (ages 6 months to 4 years)
104
Initiate empiric antibiotic and Ibuprofen
Await culture results for specific antibiotic selection
67,71,77,124
Consider PICC for prolonged IV therapy; Need ID approval for bacteremia
13,51
Decision for Surgery
No
25
Initiate empiric antibiotic and Ibuprofen; Regular diet
Yes
14,26,34,75
Incision, irrigation and debridement; Biopsy and culture; placement of drains; CRP before Surgery; Begin Empiric Antibiotic and Ibuprofen
Yes
Decision for Repeat Surgery
No
Infectious disease consultation criteria:
Persistent bacteremia (2 consecutive positive cultures)
Persistent fever; ICU admission
Atypical organisms; Resistant Organisms
Disseminated infection; Spine or Pelvis Infection
Chronic infection (> 2 weeks); Prosthetic devices; DVT
Age < 3 months; Immune Compromised Host
Send specimen for Histology, Gram Stain and Culture; Kingella kingae plated on blood agar (ages 6 months to 4 years)
5,22,85
Observe on Abx; Repeat CRP/ESR every 48 hours
Hematology consultation criteria:
Disseminated infection with persistent bacteremia or fever
and not clinically improving
Evidence of DVT or SPE
5,22,85
Observe on Abx; Repeat CRP/ESR every 48 hours
193
If not demonstrating clinical or laboratory improvement, consider surgery
Bacteremia: Should have 2 negative blood cultures for 48 hours prior to D/C
PT to evaluate for gait training; TTWB for LE osteomyelitis
Discharge Criteria:
Clinically improved
Resolved pain, afebrile
Clear by physical therapy
Home antibiotics arranged if needed
13,17,22,25,74,111
22,140
Continue IV Abx until CRP and clinical exam improved; Drain<5cc/24 hours
102,126,137,152
DVT Risk Factors:
MRSA; Age>8; CRP>8; Location: Spine/Pelvis/ Lower Extremity (Femur or Tibia)
Consider MRV or Doppler if diagnostic MRI does not identify DVT
42,94,179,183,202
Consider change to oral antibiotics
Discharge to home; Outpatient orthopedic follow-up in 1-2 weeks with repeat CRP/ ESR

Figure 4

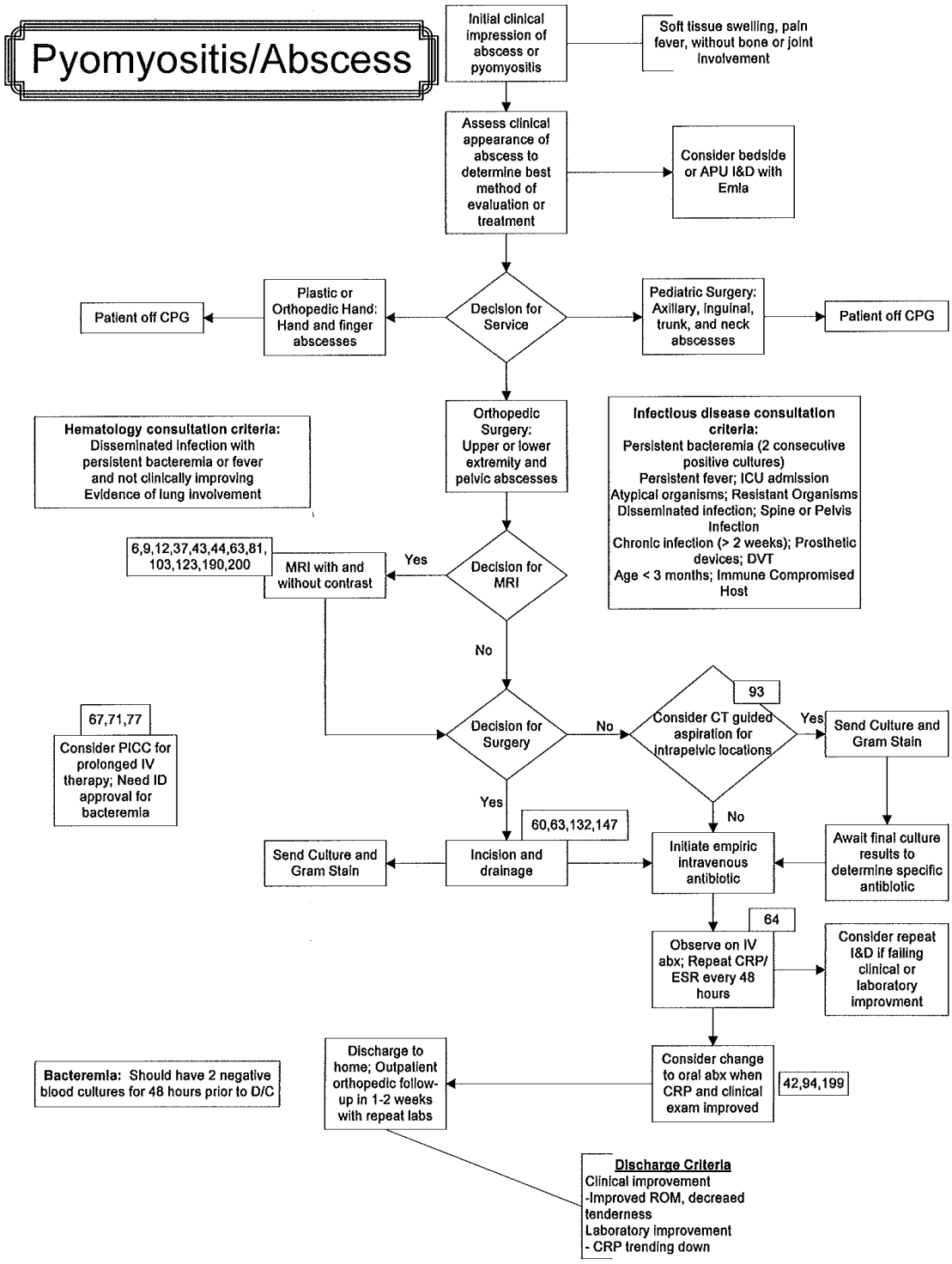

Pyomyositis/Abscess
Initial clinical impression of abscess or pyomyositis
Soft tissue swelling, pain fever, without bone or joint involvement
Assess clinical appearance of abscess to determine best method of evaluation or treatment
Consider bedside or APU I&D with Emla
Decision for Service
Plastic or Orthopedic Hand: Hand and finger abscesses
Patient off CPG
Pediatric Surgery: Axillary, inguinal, trunk, and neck abscesses
Patient off CPG
Orthopedic Surgery: Upper or lower extremity and pelvic abscesses
Hematology consultation criteria: Disseminated infection with persistent bacteremia or fever and not clinically improving Evidence of lung involvement
Infectious disease consultation criteria: Persistent bacteremia (2 consecutive positive cultures) Persistent fever; ICU admission Atypical organisms; Resistant Organisms Disseminated infection; Spine or Pelvis Infection Chronic infection (> 2 weeks); Prosthetic devices; DVT Age < 3 months; Immune Compromised Host
Decision for MRI
Yes
MRI with and without contrast
6,9,12,37,43,44,63,81, 103,123,190,200
No
Decision for Surgery
No
Consider CT guided aspiration for intrapelvic locations
93
Yes
Send Culture and Gram Stain
67,71,77
Consider PICC for prolonged IV therapy; Need ID approval for bacteremia
Yes
Incision and drainage
60,63,132,147
Send Culture and Gram Stain
No
Initiate empiric intravenous antibiotic
Await final culture results to determine specific antibiotic
Observe on IV abx; Repeat CRP/ ESR every 48 hours
64
Consider repeat I&D if failing clinical or laboratory improvment
Consider change to oral abx when CRP and clinical exam improved
42,94,199
Discharge to home; Outpatient orthopedic follow-up in 1-2 weeks with repeat labs
Bacteremia: Should have 2 negative blood cultures for 48 hours prior to D/C
Discharge Criteria
Clinical improvement
-Improved ROM, decreaed tenderness
Laboratory improvement
- CRP trending down

Figure 5

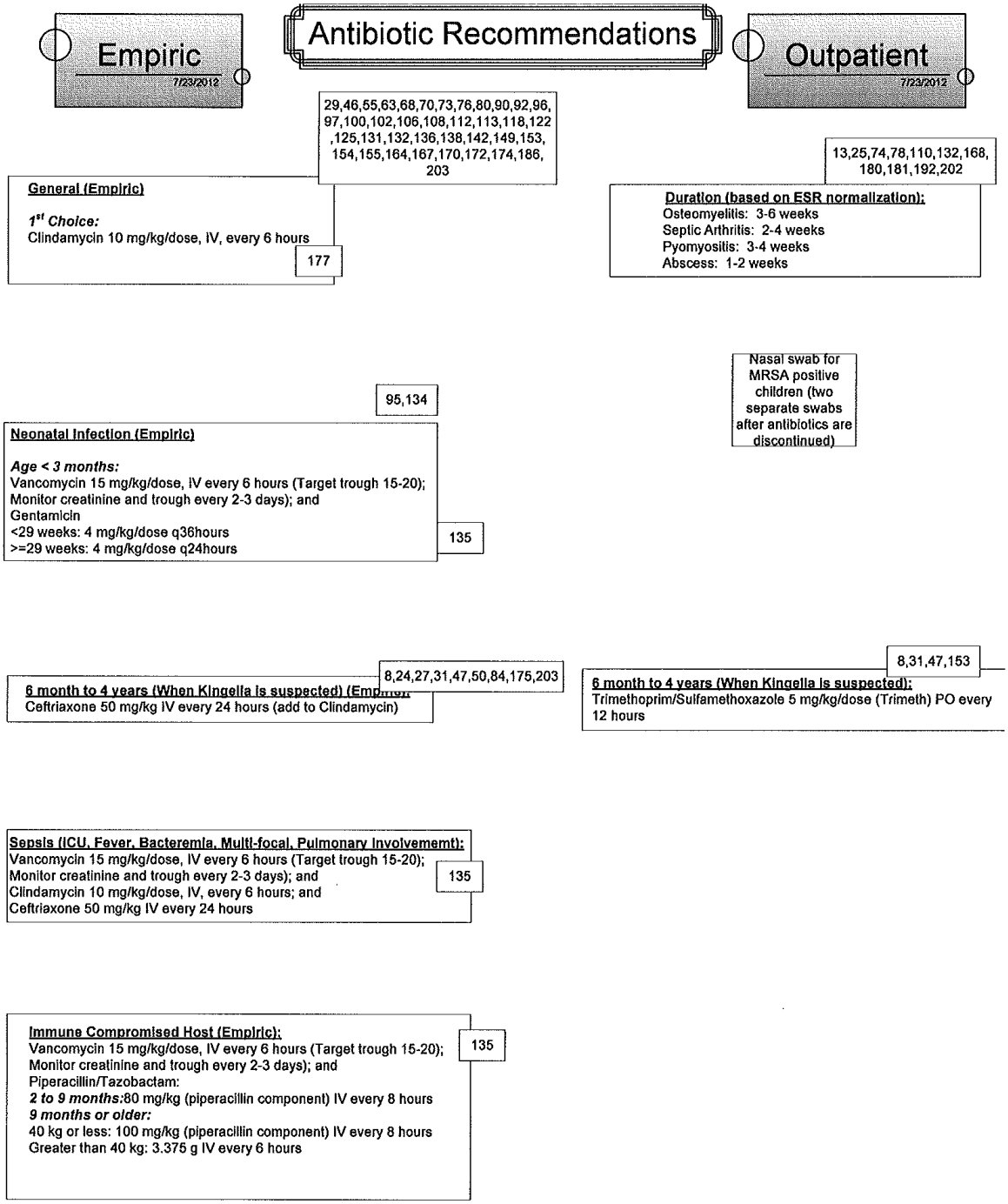
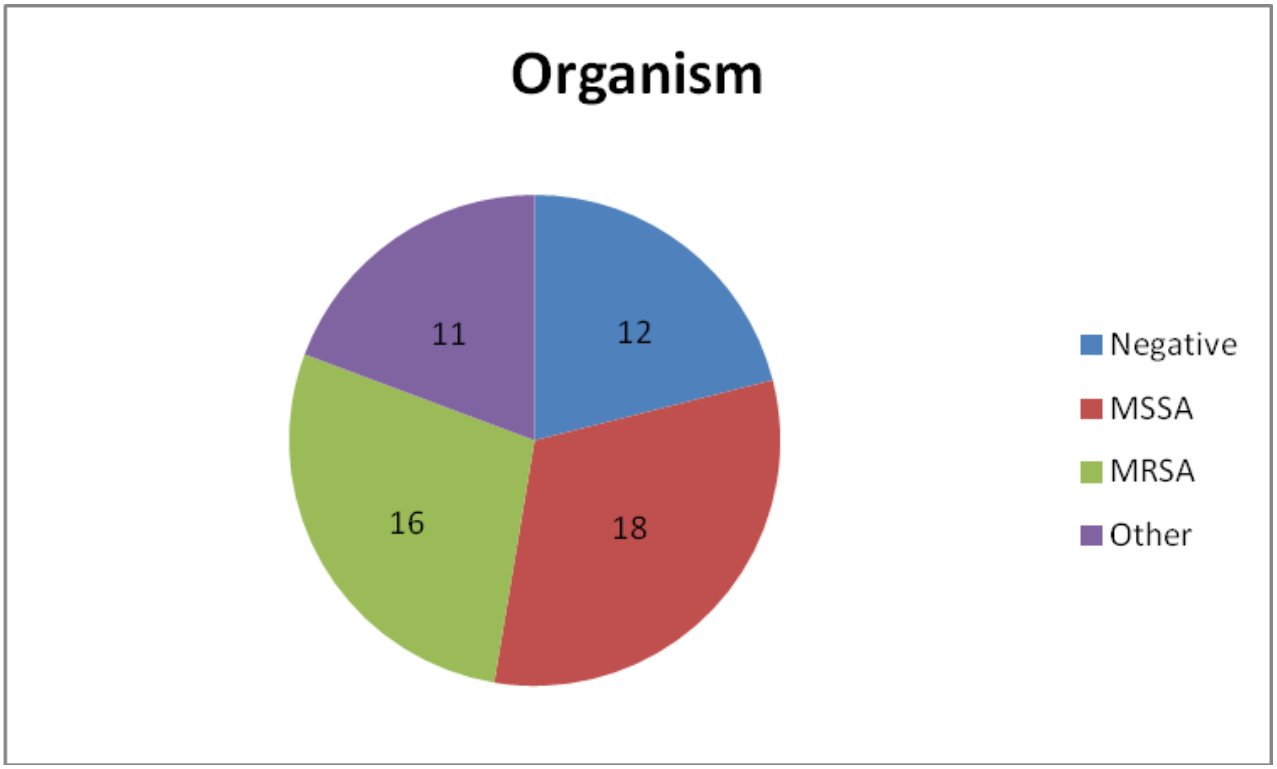

Empiric
7/23/2012
Antibiotic Recommendations
Outpatient
7/23/2012
29,46,55,63,68,70,73,76,80,90,92,96,97,100,102,106,108,112,113,118,122,125,131,132,136,138,142,149,153,154,155,164,167,170,172,174,186,203
General (Empiric)
1st Choice:
Clindamycin 10 mg/kg/dose, IV, every 6 hours
177
13,25,74,78,110,132,168,180,181,192,202
Duration (based on ESR normalization):
Osteomyelitis: 3-6 weeks
Septic Arthritis: 2-4 weeks
Pyomyositis: 3-4 weeks
Abscess: 1-2 weeks
Nasal swab for MRSA positive children (two separate swabs after antibiotics are discontinued)
95,134
Neonatal Infection (Empiric)
Age < 3 months:
Vancomycin 15 mg/kg/dose, IV every 6 hours (Target trough 15-20); Monitor creatinine and trough every 2-3 days); and
Gentamicin
<29 weeks: 4 mg/kg/dose q36hours
>=29 weeks: 4 mg/kg/dose q24hours
135
8,24,27,31,47,50,84,175,203
6 month to 4 years (When Kingella is suspected) (Empiric)
Ceftriaxone 50 mg/kg IV every 24 hours (add to Clindamycin)
8,31,47,153
6 month to 4 years (When Kingella is suspected):
Trimethoprim/Sulfamethoxazole 5 mg/kg/dose (Trimeth) PO every 12 hours
Sepsis (ICU, Fever, Bacteremia, Multi-focal, Pulmonary Involvememt):
Vancomycin 15 mg/kg/dose, IV every 6 hours (Target trough 15-20); Monitor creatinine and trough every 2-3 days); and
Clindamycin 10 mg/kg/dose, IV, every 6 hours; and
Ceftriaxone 50 mg/kg IV every 24 hours
135
Immune Compromised Host (Empiric):
Vancomycin 15 mg/kg/dose, IV every 6 hours (Target trough 15-20); Monitor creatinine and trough every 2-3 days); and
Piperacillin/Tazobactam:
2 to 9 months:80 mg/kg (piperacillin component) IV every 8 hours
9 months or older:
40 kg or less: 100 mg/kg (piperacillin component) IV every 8 hours
Greater than 40 kg: 3.375 g IV every 6 hours
135

Figure 6: Distribution of organisms in 57 children treated of acute hematogenous osteomyelitis from January 2009 to December 2009



References

1. Frank G, Mahoney HM, Eppes S. Musculoskeletal infections in children. Pediatr Clin N Am 2005; 52: 1083-1106.

2. Nelson JD. Acute osteomyelitis in children. Infect Dis Clin North Am 1990;4(3):513 –22.

3. Vaughan PA, Newman NM, Rosman MA. Acute hematogenous osteomyelitis in children. J Pediatr Orthop 1987;7:652–5.

4. Dich VQ, Nelson JD, Haltalin KC. Osteomyelitis in infants and children. Am J Dis Child 1975; 129:1273– 8.

5. Specht EE. Hemoglobinopathic salmonella osteomyelitis. Orthopedic aspects. Clin Orthop Relat Res 1971; 79:110.

6. Sexton DJ. Vascular access infections in patients undergoing dialysis with special emphasis on the role and treatment of Staphylococcus aureus. Infect Dis Clin North Am 2001; 15:731.

7. Ritz N, Curtis N. The Role of Panton-Valentine Leukocidin in Staphylococcus aureus Musculoskeletal Infections in Children. Pediatr Infect Dis J 2012; 31:514.

8. Ibia EO, Imoisili M, Pikis A. Group A beta-hemolytic streptococcal osteomyelitis in children. Pediatrics 2003; 112:e22.

9. Fitzgerald RH, Cowan JDE. Puncture wounds of the foot. Orthop Clin North Am 1975; 6(4):965–71.

10. Raz R, Miron D. Oral ciprofloxacin for treatment of infection following nail puncture wounds of the foot. Clin Infect Dis 1995;21:194– 5.

11. Lew DP, Waldvogel FA. Osteomyelitis. N Engl J Med 1997;336(14):999– 1007.

12. Gristina AG. Adherent bacterial colonization in the pathogenesis of osteomyelitis. Science 1985; 228:990– 3.

13. Lazzarini L, Mader J, Calhoun J. Osteomyelitis in long bones. J Bone Joint Surg Am 2004; 86-A(10):2305– 18.

14. Edwards MS, Baker CJ, Wagner ML, et al. An etiologic shift in infantile osteomyelitis: the emergence of the group B streptococcus. J Pediatr 1978;93(4):578 –83.

15. Asmar BI. Osteomyelitis in the neonate. Infect Dis Clin North Am 1992;6(1):117–32.

16. Christian S, Kraas J, Conway WF. Musculoskeletal infections. Seminars in Roentgenology 2007; Dept of Radiology, Medical University of South Carolina, Charleston, SC.

17. Darville T, Jacobs R. Management of acute hematogenous osteomyelitis in children. Pediatr Infect Dis J 2004;23:255– 7.

18. Mazur JM, Ross G, Cummings J, et al. Usefulness of magnetic resonance imaging for the diagnosis of acute musculoskeletal infections in children. J Pediatr Orthop 1995;15:144– 7.

19. McAndrew P, Clark C. MRI is best technique for imaging acute osteomyelitis. BMJ 1998; 316(7125):147.

20. Unkila-Kallio L, Kallio M, Eskola J, et al. Serum C-reactive protein, erythrocyte sedimentation rate, and white blood cell count in acute hematogenous osteomyelitis of children. Pediatrics 1993;92(6):800– 4.

21. Vaughan PA, Newman NM, Rosman MA. Acute hematogenous osteomyelitis in children. J Pediatr Orthop 1987;7:652–5.

22. Goldenberg, DL. Septic Arthritis. Lancet 1998; 351: 197-202.

23. Arnold SR, Elias D, Buckingham SC, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin-resistant Staphylococcus aureus. J Pediatr Orthop 2006; 26:703.

24. Corrall CJ, Merz WG, Rekedal K, Hughes WT. Aspergillus osteomyelitis in an immunocompetent adolescent: a case report and review of the literature. Pediatrics 1982; 70:455.

25. Bartkowski SB, Zapala J, Heczko P, Szuta M. Actinomycotic osteomyelitis of the mandible: review of 15 cases. J Craniomaxillofac Surg 1998; 26:63.

26. Gill FM, Sleeper LA, Weiner SJ, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative Study of Sickle Cell Disease. Blood 1995; 86:776.

27. Trueta J. The three types of acute hematogenous osteomyelitis: A clinical and vascular study. J Bone Joint Surg Br 1959; 41:671.

28. Morrey BF, Bianco AJ, Rhodes KH. Septic arthritis in children. Orthop Clin North Am 1975; 6:923– 34.

29. Greenspan A, Tehranzadeh J. Imaging of musculoskeletal and spinal infections. Radiol Clin North Am 2001;39(2):343 –55.

30. Del Beccaro MA, Champoux AN, Bockers T, et al. Septic arthritis versus transient synovitis of the hip: the value of screening laboratory tests. Ann Emerg Med 1992;21:1418–22.

31. Tindel JR, Crowder JG. Septic arthritis due to Pseudomonas aeruginosa. JAMA 1971;218(4): 559– 61.

32. Edwards MS, Baker CJ, Wagner ML, et al. An etiologic shift in infantile osteomyelitis: the emergence of the group B streptococcus. J Pediatr 1978;93(4):578 –83.

33. Gibson RK, Rosenthal SJ, Lukert BP. Pyomyositis: increasing recognition in temperate climates. The American Journal of Medicine. 1984; 77: 768-772.

34. Jayoussi R, Bialik V, Eyal A, et al. Pyomyositis caused by vigorous exercise in a boy. Acta Paediatr 1995;84:226– 7.

35. Abella BS, Kuchinic P, Hiraoka T, et al. Atraumatic clostridial myonecrosis: case report and literature review. J Emerg Med 2003;24(4):401– 5.

36. Gafur OA, Copley LA, Hollmig ST, et al. The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines. J Pediatr Orthop 2008; 28:777.

37. Harold B, Immergluck LC, Maranan MC, Lauderdale DS, et al. Community-acquired methicillin-resistant Staphylococcus aureus in children with no identified predisposing risk. JAMA 1998; 279 (8): 594-598

38. Saavedra-Lozano J, Mejias A, Ahmad N, Peromingo E, et al. Changing trends in acute osteomyelitis in children: impact of methicillin-resistant Staphylococcus aureus infections. J Pediatr Orthop 2008; 28: 569-575.

39. Martinez-Aguilar G, Avalos-Mishaan A, Hulten K, et al. Community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus musculoskeletal infections in children. The Pediatric Infectious Disease Journal 2004; 23 (8): 701-706.

40. Hollmig T, Copley L, Browne RH, Grande L, Wilson PL. Deep venous thrombosis associated with osteomyelitis in children. The Journal of Bone and Joint Surgery 2007; 89: 1517-1523.

41. Vander Have KL, Karmazyn B, Verma M, Caird MS, et al. Community-associated methicillin-resistant Staphylococcus aureus in acute musculoskeletal infection in children: a game changer. J Pediatr Orthop 2009; 29 (8): 927-931.

42. Van den Bruel A, Haj-Hassan T, Thompson M, Buntinx F, Mant D. Diagnostic value of clinical features at presentation to identify serious infection in children in develop countries: a systematic review. Lancet 2010; 375: 834-845.

43. Caird M, Flynn JM, Leung L, Millman JE, D'Italia JG et al. Factors distinguishing septic arthritis from transient synovitis of the hip in children: a prospective study. The Journal of Bone and Joint Surgery 2006; 88(6): 1251-1257.