THE CHANGING EPIDEMIOLOGY OF MUSCULOSKELETAL INFECTION IN CHILDREN: IMPACT ON EVALUATION AND TREATMENT AT A TERTIARY PEDIATRIC MEDICAL CENTER IN THE SOUTHWEST UNITED STATES

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by

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ABSTRACT

Background: Recent reports illustrate an increased incidence and severity of deep musculoskeletal infections in children. Our purpose was to review the historical experience with deep musculoskeletal infection at a tertiary pediatric medical center in the southwest United States and to compare this past experience with the more recent experience within the same institution.

Methods: A retrospective review was performed of children treated for deep musculoskeletal infection at Children's Medical Center of Dallas between January 1, 2002 and December 31, 2004. The review identified children with primary diagnoses of osteomyelitis, septic arthritis, non-tropical pyomyositis, or abscesses requiring surgical intervention. Trends were identified in terms of causative organism, anatomic location of infection, frequency of requirement of surgical debridement, and identification of adverse sequelae. These trends were compared to past experience within the same institution.

Results: 554 children were treated for deep musculoskeletal infection. Primary diagnoses were as follows: osteomyelitis – 212; septic arthritis – 118; pyomyositis – 20; and abscess – 204. The incidence of osteomyelitis rose from 11.7 cases per year, reported in 1982, to 70.7 cases per year, representing a six-fold increase. The incidence of septic arthritis rose from the 1982 report of 18.1 cases per year to 39 cases per year, a 2.2-fold increase. Staphylococcus aureus was responsible for the majority of infections, with methicillin resistant S. aureus representing an important cause of infection not identified in the previous study at this institution. The most common anatomic locations of infection occurred around the knee and hip joints. Deep venous thrombosis was

identified as the most common major complication associated with musculoskeletal infection, with 13 cases occurring over the course of the review.

Discussion: We have demonstrated a change in the epidemiology among children with musculoskeletal infection at our tertiary pediatric medical center. The marked differences that are present in our current practice when compared to the experience at the same institution over twenty years ago have prompted a detailed look into this epidemiology. The emergence of methicillin resistant *S. aureus*, the association of deep venous thrombosis musculoskeletal infection, and the reported occurrence of non-tropical pyomyositis, were unique finding in our study. Our recent experience demonstrated trends that motivated the development of clinical practice guidelines for the evaluation and treatment of pediatric musculoskeletal infection. Future prospective work will be necessary to study the success of implementation of these evidence based guidelines as well as to ascertain their merit in terms of beneficial clinical outcomes.

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Hollmig ST, Copley L, "Deep Venous Thrombosis Associated with Musculoskeletal Infection in Children." Abstract, **45th Medical Student Research Forum**, UT Southwestern Medical Center, 2007.

Hollmig ST, Copley L, Browne R, Grande L, Wilson P, "Deep Venous Thrombosis Associated with Musculoskeletal Infection in Children." Presentation, **The 29th Annual Brandon Carrell Visiting Professorship**, Texas Scottish Rite Hospital for Children, April 27-28, 2007.

Hollmig ST, Copley L, Browne R, Grande L, Wilson P, "Deep Venous Thrombosis Associated with Musculoskeletal Infection in Children." ***The Journal of Bone and Joint Surgery*. 2007; 89:1517-1523.**

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LIST OF DEFINITIONS

ABSCESS – Infection of soft tissue.

DEEP MUSCULOSKELETAL INFECTION – For this study, includes osteomyelitis, septic arthritis, non-tropical pyomyositis, and abscesses requiring operative intervention.

DVT – Deep Venous Thrombosis

GABHS – Group A Beta Hemolytic Streptococcus

MRSA – Methicillin-resistant Staphylococcus aureus

MSSA – Methicillin-susceptible Staphylococcus aureus

NON-TROPICAL PYOMYOSITIS – A primary infection of muscle in a region of temperate climate.

OSTEOMYELITIS – Infection of bone.

SPE – Septic Pulmonary Embolism

SEPTIC ARTHRITIS – Infection of the joint.

CHAPTER ONE
Introduction

THE CHANGING EPIDEMIOLOGY OF MUSCULOSKELETAL INFECTION IN PEDIATRIC PATIENTS

Deep infection of the musculoskeletal system in children includes osteomyelitis, septic arthritis, pyomyositis, and abscess. These infections typically result from hematogenous seeding of the deep tissues. Children seem to be predisposed to developing osteomyelitis and septic arthritis because of the unique circulatory pattern to the ends of long bones and joints during the period of skeletal growth.[1] Children are also more likely to be exposed to a variety of bacterial organisms which are commonly identified as the cause of deep infection. It is presumed that the increased frequency of otitis media, pharyngitis, sinusitis, bronchitis, and cellulitis during childhood as caused by staphylococcal and streptococcal organisms may be related to the timing of onset of deep musculoskeletal infection with these same organisms during childhood.[2] Children are also commonly exposed to minor traumatic injuries due to their active and aggressive lifestyle. While the relationship between trauma and musculoskeletal infection is less clearly delineated, there does appear to be a frequent concurrence between a report of trauma and the subsequent development of infection, which intuitively might be attributed to the temporary impact on the circulation of the area of injury which the trauma produces.[3-6]

It has long been reported that early recognition and prompt treatment of musculoskeletal infection are paramount to a successful clinical outcome. Delay in

diagnosis and inadequate treatment may increase the risk for adverse outcomes and long-term sequelae including chronic infection, antibiotic resistance, and sepsis from disseminated infection[7]. The principles of effective evaluation and treatment which have evolved to the present include: early recognition of the signs and symptoms of deep musculoskeletal infection, prompt initiation of appropriate empiric antibiotic therapy after an initial attempt to obtain culture material from the site of infection, sustained antibiotic treatment directed toward the specific causative organism until resolution of the infection, and surgical debridement whenever antibiotic therapy alone would be inadequate to resolve the infection.

The epidemiology of musculoskeletal infection is evolutionary in nature. There are regional, seasonal, and bacteriological variances in the types of musculoskeletal infection found in any given community. While some reports suggest a stable or declining incidence of these infections, others have identified worrisome trends to suggest a rise in the incidence of resistant organisms, a rise in the primary infection of muscle, as well as an increase in adverse sequelae such as chronic infection and deep venous thrombosis[7-10]. The purpose of this summary is to review the historical experience with deep musculoskeletal infection at a tertiary pediatric medical center in the southwest United States and to compare this past experience with the more recent experience within the same institution[11]. The trends identified in terms of causative organism, anatomic location of infection, frequency of the requirement for surgical debridement, and the identification of adverse sequelae are described in chapter two. These trends are used to create a guideline for the evaluation and treatment of deep infection of the musculoskeletal system in children; a prospective algorithm is delineated

in chapter five. While such a guideline may appear to be limited to a specific subset of patients within the facility from which it is derived, it is probable that the key features of this guideline will be more broadly transferable to other institutions in which a comparable spectrum of disease is encountered.

Over the course of formulating a broad review of all musculoskeletal infections treated at our institution, two specific topics were identified as warranting a more comprehensive evaluation. The association between deep musculoskeletal infection and deep venous thrombosis (DVT) and septic pulmonary embolism (SPE) is discussed in chapter three. The emergence of primary, non-tropical pyomyositis is described in chapter four.

CHAPTER TWO
Epidemiology of Musculoskeletal Infection in Children at Children's Medical Center of Dallas, 2002-2004

BACKGROUND

In 1982, Mary Anne Jackson and John Nelson reported on the experience in managing acute infections of bone and joint in a pediatric population at the Children's Medical Center and Parkland Memorial Hospital in Dallas[11]. Over a 26 year period, 471 children (18.1 cases per year) were treated for septic arthritis. Additionally, 258 children with osteomyelitis (11.7 cases per year) were reported over a 22 year period[11]. While data from this early publication is limited to medical management of septic arthritis and osteomyelitis, certain trends in terms of causative organism, location of infection, and response to treatment can be compared to the experience at the same institution over two decades later.

Recent clinical experience suggests that there has been a considerable change in the epidemiology of musculoskeletal infection in comparison to that reported by Jackson and Nelson. The purpose of this chapter is to report the current experience in the evaluation and treatment of the full spectrum of deep musculoskeletal infection in children treated at the Children's Medical Center of Dallas. Whenever possible, historical comparison will be made to the experience at the same institution reported in 1982.

METHODS

Medical records of children who were evaluated and treated for infection involving the spine, pelvis, upper or lower extremities in the emergency room or inpatient hospital of the Children's Medical Center of Dallas were retrospectively reviewed from the period between January 1, 2002 and December 31, 2004. Multiple data fields were recorded including: patient demographics, insurance class, age at admission, date of symptom onset, prior evaluation or treatment, history of trauma, history of fever, history of non-weight bearing, history of upper respiratory illness, primary musculoskeletal infection diagnosis, location of infection, secondary musculoskeletal infection diagnoses, concurrent medical conditions, vital signs, radiographic studies and results, laboratory studies and results, culture results, dates of admission and discharge, consultations obtained, surgical procedures performed, and complications.

Emergency room care was assessed for diagnoses and treatments of infections involving the spine, pelvis or extremities which did not fall into one of the four primary diagnostic categories of osteomyelitis, septic arthritis, pyomyositis or abscess requiring operative intervention. The emergency room patients were categorized as: cellulitis treated as outpatient with oral antibiotic, cellulitis requiring inpatient antibiotic, abscesses treated with incision and debridement in the emergency room and discharged with oral antibiotic, or abscesses treated with incision and debridement in the emergency room or hospital bedside requiring inpatient antibiotic.

Children with deep musculoskeletal infection were categorized with respect to the primary diagnosis of osteomyelitis, septic arthritis, pyomyositis, or abscess. Comparison

was made between children with these main diagnostic categories with respect to laboratory values, culture results, requirement for surgical procedures, development of complications, and length of hospital stay.

Population data was obtained from the United States Census board for the periods inclusive of 1960-1980 and 2002 -2004 for the counties including Dallas, Collin, Denton, Rockwall, Kaufman, and Ellis.

RESULTS

Between January 1, 2002 and December 31, 2004 there were 3,328 children who were evaluated at the Children's Medical Center of Dallas and treated for infection involving the spine, pelvis, or extremities. Of these, 1,086 children were diagnosed with cellulitis and treated as outpatients with oral antibiotics. An additional 316 children with cellulitis were admitted for a brief course of intravenous antibiotic as hospital inpatients. There were 1271 children with abscesses who were treated with incision and drainage in the emergency room and sent home on oral antibiotics. There were 99 children with abscesses who underwent emergency room or hospital bedside incision and drainage followed by a brief course of intravenous antibiotics as inpatients. The remaining 554 children were identified as having a deep musculoskeletal infection and classified according to the primary diagnoses of osteomyelitis (212), septic arthritis (118), pyomyositis (20), and abscess requiring surgical drainage in the operating room (204). It should be noted while many children presented with an infection which was isolated to the primary diagnostic category there were a number of children who were identified as having infection which involved multiple tissue locations. Magnetic resonance imaging

(MRI) reports and operative reports were utilized to identify the nature and frequency of overlapping infection diagnoses. Table 1 summarizes this interrelationship between primary and secondary diagnoses among the 554 children with deep musculoskeletal infection.

Table 1. Diagnostic classification of deep musculoskeletal infection

Complete Diagnosis	
Osteomyelitis, septic arthritis, pyomyositis, abscess	6
Osteomyelitis, septic arthritis, pyomyositis	3
Osteomyelitis, septic arthritis, abscess	1
Osteomyelitis, pyomyositis, abscess	11
Osteomyelitis, septic arthritis	15
Osteomyelitis, pyomyositis	11
Osteomyelitis, abscess	45
Osteomyelitis	112
Septic Arthritis, pyomyositis, abscess	2
Septic Arthritis, pyomyositis	1
Septic Arthritis, abscess	8
Septic Arthritis	106
Pyomyositis, abscess	11
Pyomyositis	9
Abscess	206

The regional referral patterns of children with musculoskeletal infection to Children's Medical Center of Dallas are illustrated in figure 1. The majority of children were noted to reside in the Dallas Metroplex. Dallas County residents comprise 395 of the 551 (71.7%) children in our study who had recorded zip codes. The region including Dallas (considered zone 1), Collin and Denton (zone 2), and Rockwall, Kaufman, and Ellis counties (zone 3) contributed 483 of 551 children (87.6%). Finally, widening the

referral map to include the surrounding fourteen counties captured 533 of the 551 children (96.7%)

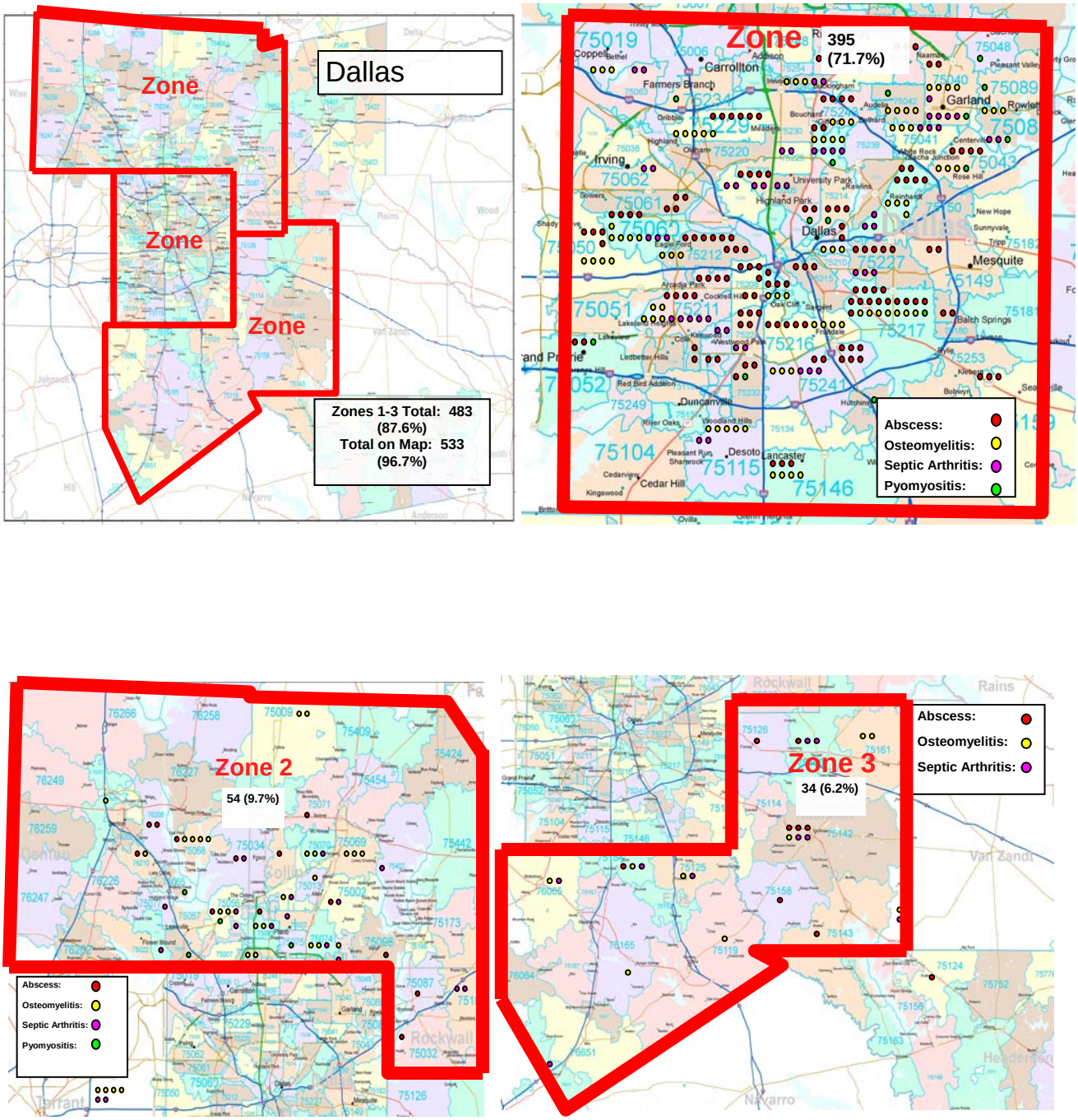


Figure 1. Zip code distribution of musculoskeletal infection.

The United States Census Board indicated that the population for the local referring counties had been, on average, 1,687,122 between the years 1960 and 1980. In

comparison, the average population between the years 2002 and 2004 was reported as 3,651,037, a 2.2 fold increase.

The seasonal timing of presentation of deep infection to Children's was also recorded. In total there were 600 admissions for the 554 children with deep musculoskeletal infection. Of these admissions, 360 (60%) occurred during the six month period from May through October, inclusive.

During the evaluation and treatment of the 554 children with musculoskeletal infection, a total of 1844 radiologic procedures were performed. The most common study obtained was the plain radiograph (1106), followed in incidence by MRI (366), ultrasound (148), bone scan (145) and CT scan (74). Three children had Doppler ultrasounds and two children had echocardiograms.

The relative utility of the various forms of radiographic studies was assessed by determining the relative percentage of findings which were considered "normal" as interpreted by the radiologist, versus those studies which resulted in an interpretation other than "normal". Of the studies frequently performed, plain radiographs yielded the largest percentage of "normal" interpretations (516 of 1106, or 46.7%). Whereas MRI studies were most likely to result in varying interpretations with "normal" readings identified in only 11 of 366 (3%). Ultrasound yielded negative readings in 42 of 148 studies (28.4%). Bone scan and CT scans were interpreted as "normal" in 14 of 145 (9.7%) and 8 of 66 (10.8%) studies, respectively.

A variety of cultures were sent to microbiology for analysis, including aerobic (1610), anaerobic (544), fungal (178), acid fast bacteria (AFB) (137), gonococcal (GC) (13), Bartonella (3), viral (1), and lyme (1) for a total of 2487 cultures. Of the cultures

sent, positive results were identified in 663 out of 2487 (26.7%). Aerobic cultures were positive in 622 of 1610 (38.6%) samples; anaerobic cultures were positive in only 15 of 544 (2.8%) samples; fungal cultures were positive in 12 of 178 (6.7%) samples; AFB cultures were positive in only 4 of 137 (2.9%); GC cultures were positive in 3 of 13 (23.1%) samples; Bartonella cultures were positive in 2 of 3 (66.7%) samples; viral and lyme titers (1 each) were each negative.

There were 801 blood cultures sent from the 554 children who had deep musculoskeletal infections. Blood cultures were positive in 155 (19.4%) of samples.

Osteomyelitis

Among the 212 children with a primary diagnosis of osteomyelitis there were six children with discitis/vertebral osteomyelitis. Children with osteomyelitis had a mean age of 7.7 years, ranging from 3 weeks to 17.9 years of age. The children with discitis/vertebral osteomyelitis had a mean age of 5 years, with a range from 1.6 to 14.3 years. Table 2 demonstrates the frequency distribution of anatomic locations of osteomyelitis. The most common areas of involvement were the proximal femur (24), distal femur (24), the pelvis (21), distal tibia (20), proximal tibia (18), and the calcaneus (16). A comparison is made to the location findings of Jackson and Nelson in table 2.

Table 2. Foci of osteomyelitis

Children's 2002-2004		**Jackson and Nelson**	
Location	Number	Location	Number
Pelvis			
Acetabulum	1		
Ischium	3	Ischium	6
Iliac	1	Ilium	4
Pelvis, unspecified	7		
Pubic	4		
Sacrum	5	Sacrum	3
Thigh			

Distal Femur	24	Femur	72
Proximal Femur	24		
Leg			
Distal Fibula	12		
Proximal Fibula	2	Fibula	33
Distal Tibia	20	Tibia	62
Proximal Tibia	18		
Proximal Tibia and Fibula	4		
Distal Tibia and Fibula	4		
Mid Tibia and Fibula	1		
Foot			
Great Toe	4		
Talus	1		
Toe	9		
Calcaneus	16	Calcaneus	10
Cuboid	2	Cuboid	1
Navicular	1	Cuneiform	1
Metatarsal	13	Metatarsal	5
Clavicle	3	Clavicle	3
Arm			
Proximal Humerus	6		
Distal Humerus	5		
Forearm and Hand			
Finger	7	Phalanx	11
Wrist	1	Carpal bone	2
Metacarpal	3	Ulna	10
Distal Radius	6	Radius	12

Of the 206 children with osteomyelitis which did not involve the spine, 191 (92.7%) cases were considered to involve a single location, whereas the remaining 15 (7.3%) were considered to be multi-focal. Septic arthritis occurring in the adjacent joint as a contiguous infection was identified in 31 children (15%).

Of the children with osteomyelitis, 41% reported a history of trauma, 69% reported a history of fever, 47% reported a history of non-weight bearing, and 82% reported pain. Only 19% reported a recent history of upper respiratory illness. Prior medical evaluation had been performed in 84% of these children and the mean duration

from the onset of symptoms until the time of admission to Children's Medical Center was 16.7 days for osteomyelitis and 13.2 days for discitis/vertebral osteomyelitis.

At the time of initial evaluation, children with osteomyelitis had a mean temperature of 37.2 degrees Celsius, a mean white blood cell (WBC) count of 8.0 x 10^9/L, a mean C-reactive protein (CRP) of 3.3 mg/dL (range 0.4 to 34.8), and a mean erythrocyte sedimentation rate of 39.5 mm per hour (range 1 to 140).

The causative organisms for osteomyelitis are listed in table 3. No organism was identified in 78 (36.8%) of the infections. The most commonly identified organisms were *S aureus* (98), GABHS (9), and *P aeruginosa* (9). Among *S aureus* species (98 total), 45 (46%) were classified as Methicillin-sensitive; 44 (45%) were classified as Methicillin-resistant; and 9 (9%) were classified as coagulase negative. A comparison is made to the causative organism of osteomyelitis in the work of Jackson and Nelson in table 3.

Table 3. Primary organism causing osteomyelitis

Primary Causative Organism	Children's 2002-2004	Jackson and Nelson
No growth	72	64
Total Staphylococcus aureus	99	163
MSSA	45	
MRSA	44	
GABHS	9	23
Pseudomonas aeruginosa	9	4
Staphylococcus aureus, coagulase negative	9	
No cultures sent	6	
Enterobacter cloacae	3	
Kingella kingae	3	
Bartonella henslae	1	
Candida tropicalis	1	
Coccidioides immitis	1	
E. coli	1	3
Eikenella corrodens	1	
Enterococcus	1	
Fusarium species	1	
Gram positive cocci	1	
Gram positive rods	1	
Group B streptococcus	1	3
Salmonella	1	3
Streptococcus pneumoniae	1	5
Haemophilus influenza		8
Total Cases of Osteomyelitis	212	258

There were 36 different antibiotics selected during the course of treatment of the 206 children with osteomyelitis not involving the spine. The most commonly selected antibiotics were vancomycin, cefazolin, cephalexin, clindamycin, and rifampin.

Children with discitis/vertebral osteomyelitis were treated with eight different antibiotics throughout their illness. The most common selections were vancomycin, rifampin, cefazolin, and trimethoprim/sulfamethoxazole. The mean duration of intravenous antibiotic use was 9.5 days for children with osteomyelitis and 8.3 days for children with discitis/vertebral osteomyelitis.

A total of 253 surgical procedures were performed on 114 of the 212 (53.8%) children with osteomyelitis. The remaining 98 (46.2%) of children with osteomyelitis had an appropriate response to antibiotics alone. Of the children who underwent surgery, 56 (49.1%) required only one surgical procedure, 30 (26.3%) required two procedures, and 14 (12.3%) required three procedures. There were 14 additional children (13.3% of those who underwent surgery) who required multiple surgical procedures (range 4-11 procedures), in order to adequately treat their infection.

Children with osteomyelitis had 234 separate hospitalizations for their infections. The mean length of hospitalization was 11 days (range 0-90 days).

Septic Arthritis

Children with septic arthritis had a mean age of 6.1 years, ranging from 2 weeks to 17.7 years of age. The most common areas of involvement were the hip (51), knee (45), elbow (10), ankle (5), and shoulder (3).

Table 4. Primary foci of Septic Arthritis

Location	Children's 2002-2004	Jackson and Nelson
Lower Extremity		
Hip	51	116
Sacrum	1	2
Knee	45	213
Ankle	5	70
Toe	1	
Metatarsal		4
Upper Extremity		
Shoulder	3	18
Acromioclavicular		1
Elbow	10	64
Wrist	1	22
Metacarpal		1
Interphalangeal		4
Total Cases of Septic Arthritis	118	471

Of the 118 children with septic arthritis, 19% reported a history of trauma, 62.5% reported a history of fever, 62.5% reported a history of non-weight bearing, and 86% reported pain. Only 19% reported a recent history of upper respiratory illness. Prior medical evaluation had been performed in 62.5% of these children and the mean duration from the onset of symptoms until the time of admission to Children's Medical center was 5.2 days for septic arthritis (range 0 to 40 days).

At the time of initial evaluation, children with septic arthritis had a mean temperature of 37.2 degrees Celsius, a mean white blood cell (WBC) count of 9.0 x 10^9/L, a mean C-reactive protein (CRP) of 4.7 mg/dL (range 0.5 to 33.9), and a mean erythrocyte sedimentation rate of 50.2 mm per hour (range 1 to 140).

The causative organisms for septic arthritis were recorded. No organism was identified in 72 (61.5%) of the infections. The most commonly identified organisms were *S aureus* (22), GABHS (7), and *S pneumoniae* (5). Among *S aureus* species (22 total), 14 (64%) were classified as Methicillin-sensitive; 5 (23%) were classified as Methicillin-resistant; and 3 (13%) were classified as coagulase negative.

A total of 27 different antibiotics were selected in treating septic arthritis, with the most common being: cefazolin, cephalexin, vancomycin, and clindamycin. The mean duration of intravenous antibiotic use for children with septic arthritis was 6.6 days.

A total of 149 surgical procedures were performed on 110 of the 118 (94%) children with septic arthritis. The remaining 7 (6%) of children with septic arthritis had an appropriate response to antibiotics and joint aspiration. Of the children who underwent surgery, 87 (79.1%) required only one surgical procedure, 12 (10.9%) required two procedures, and 8 (7.3%) required three procedures. There were 3 additional children (2.7% of those who underwent surgery) who required multiple surgical procedures (range 4-5 procedures), in order to adequately treat their infection.

Children with septic arthritis had 119 separate hospitalizations for their infections. The mean length of hospitalization was 6.4 days (range 0-40 days).

Non-tropical Pyomyositis

Children with pyomyositis had a mean age of 6.6 years, ranging from 6 months to 17.6 years of age. Table 5 demonstrates the frequency distribution of anatomic locations of pyomyositis. The most common areas of involvement were the leg (6), hip (4), and thigh (3).

Table 5. Foci and causative organism in non-tropical pyomyositis

Patient #	Location of Pyomyositis	Organism
25	L Leg (anterior and lateral compartments)	GABHS
111	R soleus and flexor hallucis longus	MSSA
112	L Iliopsoas, adductor and flexor musculature	No Growth
120	BL gastrocnemius and soleus, R peroneus longus and brevis	Gram Positive Cocci
121	R Hip	No Growth
140	R soleus	Staphylococcus aureus (coagulase negative)
149	R subclavius and subscapularis	No Growth
227	L SCM	No Growth
240	R adductor longus, obturator internus and externus	MSSA
244	L semimembranosus	MRSA
251	R iliopsoas	MRSA
370	L Gastrocnemius	Streptococcus milleri
400	Muscles of R popliteal fossa	No Growth
437	R tensor fascia lata, vastus medialis and lateralis	No Growth
469	R semimembranosus	MRSA

483	R psoas major, tensor fascia lata, vastus lateralis, rectus femorus	No Cultures Sent
484	R extensor digitorum longus and soleus	No Growth
486	L triceps and L flexor forearm	GABHS
490	R flexor digitorum	MRSA
523	R flexor hallucis longus	MSSA

Of the 20 children with pyomyositis as a primary diagnosis, 13% reported a history of trauma, 79% reported a history of fever, 37.5% reported a history of non-weight bearing, and 92% reported pain. Only 13% reported a recent history of upper respiratory illness.

Prior medical evaluation had been performed in 62.5% of these children and the mean duration from the onset of symptoms until the time of admission to Children's Medical center was 9.4 days for pyomyositis (range 0 to 120 days).

At the time of initial evaluation, children with pyomyositis had a mean temperature of 37.4 degrees Celsius, a mean white blood cell (WBC) count of 11.7 x 10^9/L, a mean C-reactive protein (CRP) of 5.0 mg/dL (range 0.5 to 31.9), and a mean erythrocyte sedimentation rate of 41.3 mm per hour (range 8 to 83).

The causative organisms for pyomyositis are listed in table 5. No organism was identified in 7 (31.8%) of the infections. The most commonly identified organisms were *S aureus* (9), and GABHS (2). Among *S aureus* species (9 total), 3 (33%) were classified as Methicillin-sensitive; 5 (56%) were classified as Methicillin-resistant; and 1 (11%) was classified as coagulase negative. No cultures were sent in one case.

A total of 19 different antibiotics were used during the course of treatment of the 20 children who had a primary diagnosis of pyomyositis. The most commonly used antibiotics included: cefazolin, vancomycin, cephalexin, and clindamycin. The mean duration of intravenous antibiotic use for children with pyomyositis was 5.9 days.

A total of 31 surgical procedures were performed on 15 of the 20 (67%) children with pyomyositis. The remaining 2 (33%) of children with pyomyositis had an appropriate response to antibiotics alone. Of the children who underwent surgery, 10 (66.7%) required only one surgical procedure, 2 (13.3%) required two procedures, and 3 (15%) required three or more procedures (range 3-8).

Children with pyomyositis had 24 separate hospitalizations for their infections. The mean length of hospitalization was 8.0 days (range 1-30 days).

In addition to the 20 children who had a primary diagnosis of pyomyositis, there were 33 children who had other primary musculoskeletal diagnoses, but who were also identified as having pyomyositis as a component of their clinical condition.

Abscess

There were 204 children with deep abscesses involving the musculoskeletal system who required surgical drainage in the operating room. They had a mean age of 6.4 years, ranging from 2 weeks to 18 years of age. Table 6 demonstrates the frequency distribution of anatomic locations of the abscesses. The most common areas of involvement were the groin (46), thigh (33), foot (18), and buttock (16). Of the abscesses, 200 (98%) were considered to be isolated to a single location, whereas 4 (2%) were identified as multi-focal. In addition to the 204 children in whom an abscess was considered to be the primary diagnosis, there were 76 children who were identified as having an abscess as a discrete component of other primary musculoskeletal infections.

Table 6. Foci of abscesses

Upper Extremity	Number	Lower Extremity	Number
Shoulder	2	Hip	5
Axilla	10	Pubis	2
Arm	12	Perineum	2
Elbow	3	Buttock	18
Forearm	6	Groin	46
Hand	7	Thigh	33
Thumb	1	Knee	8
Finger	5	Prepatellar	3
		Leg	13
		Calf	8
		Ankle	2
		Foot	18
		Toe	1

Of the 204 children with abscess, 28.5% reported a history of trauma, 60% reported a history of fever, and 78.5% reported pain. Only 9.3% reported a recent history of upper respiratory illness and only 16% reported a history of non-weight bearing. Prior medical evaluation had been performed in 63.6% of these children and the mean duration from the onset of symptoms until the time of admission to Children's Medical center was 6.6 days (range 0 to 107 days).

At the time of initial evaluation, children with abscesses had a mean temperature of 37.2 degrees Celsius, a mean white blood cell (WBC) count of 14.2 x 10^9/L, a mean C-reactive protein (CRP) of 3.7 mg/dL (range 0.5 to 24.9), and a mean erythrocyte sedimentation rate of 35.2 mm per hour (range 1 to 120).

The causative organisms for abscesses were recorded. No organism was identified in 27 (13%) of the infections. The most commonly identified organisms were *S aureus* (151), GABHS (11), and Group G Streptococcus (3). Among *S aureus* species (151 total), 34 (22.5%) were classified as Methicillin-sensitive; 112 (74.2%) were classified as Methicillin-resistant; and 5 (3.3%) were classified as coagulase negative.

Antibiotic selection for the treatment of children with deep abscesses was reviewed. A total of 24 different antibiotics were used during the course of treatment of

the 204 children who had a primary diagnosis of abscess. The most commonly used antibiotics included: cefazolin, clindamycin, vancomycin, rifampin, and trimethoprim/sulfamethoxazole. The mean duration of intravenous antibiotic use for children with abscess was 3.9 days.

A total of 227 surgical procedures were performed on 201 of the 204 (98.4%) children with abscesses. The remaining 4 (1.6%) children with a primary diagnosis of abscess had an appropriate response to antibiotics alone. Of the children who underwent surgery, 179 (88%) required only one surgical procedure, and 23 (11.4%) required two procedures. Only one child required more than two surgical procedures (four) to resolve the abscess.

Children with abscesses had 214 separate hospitalizations for their infections. The mean length of hospitalization was 3.6 days (range 0-26 days).

DISCUSSION

The evolutionary nature of the epidemiology of musculoskeletal infection in children is not surprising. Numerous factors may play a role in affecting changes within a community which can alter the local experience of a condition as diverse as musculoskeletal infection. Population growth, local referral patterns, appearance of antibiotic resistant organisms (MRSA), and the recrudescence of specific bacterial infections as a consequence of immunizations (*Haemophilus influenza*, type b) name only a few of these factors. [8, 12-16] The recognition of change in the epidemiology of musculoskeletal infection within a community may be important if the current experience substantially differs from the historical experience so as to potentially alter the treatment

algorithms, practice habits, and treatment guidelines which are followed by the physicians within that community[17]. We believe that the findings of our retrospective review demonstrate a substantial change in the epidemiology of musculoskeletal infection at our tertiary pediatric medical center. We have identified an increased incidence of osteomyelitis and septic arthritis in comparison to the experience reported at the same institution nearly two decades prior. We have identified and reported other forms of deep musculoskeletal infection (pyomyositis and deep abscesses) which are relevant to the orthopedic community in terms of their incidence, clinical significance, and treatment. We have also delineated the inter-relationship which the major subtypes of musculoskeletal infection may have, and have attempted to categorize these overlapping categories of infection so as to demonstrate the importance of thorough diagnostic evaluation to enable correct diagnosis and treatment. We have demonstrated the current microbiology within each primary diagnostic category which may help to guide rational empiric antibiotic selection within this specific community as well as in other communities and institutions in which a similar spectrum of disease is encountered. Based on all of these findings, we believe that our report should alter the treatment algorithms, practice habits, and treatment guidelines which are followed by the physicians within this institution, community and geographic region.

The incidence of osteomyelitis rose from 11.7 cases per year, reported in 1982, to 70.7 cases per year in recent years, representing a six-fold increase. The incidence of septic arthritis rose from the 1982 report of 18.1 cases per year to our more recent report of 39 cases per year, a 2.2-fold increase. The population of the six counties from which the majority of referrals were made demonstrated a similar 2.2-fold increase. While this

population increase may adequately support the increased incidence of septic arthritis in our institution, it does not suitably explain the much higher rate of referral of osteomyelitis during the same timeframe.

Another possible explanation for the increased referral of musculoskeletal infection, specifically osteomyelitis, to Children's Medical Center of Dallas in recent years was the creation of an independent pediatric emergency room with increased public visibility of the facility as a referral center. However, we believe this is only a partial explanation for the phenomenon of a six-fold increase in the incidence of osteomyelitis. Additional factors, such as an increase in the severity and complexity of these illnesses related to the emergence of MRSA, are likely to play a role in motivating such a change in referral pattern. Unfortunately, our data does not lend itself to the evaluation of these factors. While we believe that the necessity of surgery in the treatment of osteomyelitis has increased as recently as the past decade, likely as a consequence of an increase in the severity of disease, we do not have comparative data from Jackson and Nelson so as to confirm this clinical impression [18-21.]

The inter-relationship and overlap of musculoskeletal infection diagnostic categories is a noteworthy finding in this study. Previous reports focused attention on the sequela-prone child who was likely to have contiguous osteomyelitis and septic arthritis[7]. In recent decades the paradigm of musculoskeletal infection has been confined to these two entities with a small degree of overlap. Our research lends support to a more comprehensive paradigm which takes into account each of the primary diagnostic categories as well as the subcategories which result from the presence of multiple diagnoses within individual patients. From a clinical perspective, it is relevant to

determine which children may have an isolated septic arthritis, which requires approximately 3-4 weeks of antibiotic therapy, versus one who has an associated osteomyelitis, which may require 4-6 weeks of antibiotic therapy[7, 11, 22--28, 29]. Additionally, it is important to identify, early in the course of hospitalization, which children have abscesses associated with any of the primary forms of musculoskeletal infection as it is most likely that these children will fail to have clinical or laboratory improvement without surgical intervention.

The underlying assumption in our categorization of associated primary, secondary, tertiary, and quaternary infection diagnoses is that infection most likely begins in one tissue type and then secondarily extends to the adjacent tissues, either directly or through contiguous vascular or lymphatic, channels. We believe that there is likely a hierarchy of tissue types in which the infection is more likely to occur primarily given the nature of the tissues involved and the likelihood of secondary spread to adjacent structures. Therefore we ordered the types of primary infection as follows: bone>joint>muscle>soft tissue. We believe that it is more likely that an osteomyelitis would extend into an adjacent joint, via a breach in the metaphyseal integrity in an intracapsular location, than vice versa[30-31]. Because joint fluid is inhibitory of bacterial growth, an infection in this location is less likely than that occurring in bone to rapidly extend to adjacent tissues. Muscle, because of its rich blood supply, is even further resistant to the onset of infection, much less than to serve as an avenue of rapid spread to adjacent structures.[32] This is somewhat borne out by the lower incidence of the primary diagnosis of pyomyositis in our series compared to that of osteomyelitis or septic arthritis.

We believe that there is an association between the extent of musculoskeletal infection, as it pertains to the involvement of multiple tissue types, and the clinical severity of infection. For this reason, we believe that it is relevant to ascertain the specific diagnoses, primary and secondary, of musculoskeletal infection early in the course of hospitalization so as to guide therapy and anticipate the clinical response. In order to accomplish this, an MRI should be obtained earlier during the course of hospitalization than our current clinical practice habits and algorithms suggest. In doing so, it may be possible to forego other studies, such as bone scintigraphy, which may historically have been relied upon as an inexpensive and more convenient diagnostic tool. We currently favor MRI, which gives a more detailed picture of the spatial extent of the inflammatory response within the involved tissues.[33] Further prospective work will be necessary to demonstrate the clinical benefits, in terms of the potential for reduced number of surgical procedures and length of hospitalization in light of such a modification in our clinical practice protocols.

The spectrum of bacterial organisms as the cause of the various musculoskeletal infections in children has changed over the past two decades. Most obvious is the dramatic reduction in the incidence of *H influenzae*, type b infections. Of greater importance is the advent of community acquired MRSA infections.[8, 12-14, 16, 34] With these findings, the selection of empiric antibiotic should necessarily change so as to adequately cover for the relative incidence of MRSA within each primary diagnostic category. Historically, a first generation cephalosporin or a semi-synthetic penicillin was adequate to cover the majority of bone and joint infections. Currently, this form of treatment would likely have been inadequate for 44 of the 212 (20.8%) children with

osteomyelitis, 5 of the 118 (4.3%) children with septic arthritis, 5 of the 20 (25%) children with pyomyositis, and 112 of the 204 (55.4%) children with deep abscesses in our study. Additionally, if we include the 2 children with GABHS pyomyositis, which does not respond well to cephalosporins or penicillins, then the percentage of children with pyomyositis who would be inadequately treated rises to 35%.

With the exception of septic arthritis, each of the primary musculoskeletal diagnoses represents an incidence of MRSA infection above 20%. This is ample evidence to suggest a change in the current practice guidelines within our specific institution and recommend empiric antibiotic therapy with adequate coverage of MRSA. Further evidence of this is given by the demonstrated spectrum of antibiotic therapy which was selected in the treatment of these infections within the study period. Given the wide variety of antibiotic selections, it is unlikely that there is a clear practice habit which has been demonstrated within the institution to this date. Our study, therefore, suggests that there may be benefit in establishing a clinical practice guideline with rational empiric antibiotic selections for each primary diagnostic category and educating the hospital based physicians of these guidelines so as to improve compliance and thereby create a new practice habit.

Surgical procedures represent a substantial commitment of resources and time in the treatment of children with infection. While it is not possible to determine whether our current rate of surgery for children with musculoskeletal infection has changed in comparison to that performed twenty years ago, it is possible to speculate that the current number of surgical procedures may be reduced by implementing the aforementioned practice improvements within our institution. Prompt administration of an antibiotic

appropriate to treat the most likely causative organism would likely pre-empt surgical intervention in some children. Early adequate visualization of the extent and nature of the inflammatory response in all of the involved tissue planes with MRI would also guide a more thorough and accurate debridement during the earliest surgical procedure(s) so as to prevent the need for multiple procedures in a given child.

Laboratory cultures may represent an additional resource which our study indicates may be improperly utilized in the evaluation of children with musculoskeletal infection. The exceedingly low yield for certain culture types (anaerobic, fungal, and AFB) would suggest that these cultures should be sent only under circumstances in which a high index of suspicion exists. Certainly, if a positive culture has already been obtained in a child with a specific diagnosis, then repeatedly sending anaerobic cultures during follow-up débridements is irrational and unnecessary.

In summary, we have demonstrated a change in the epidemiology among children with musculoskeletal infection at our tertiary pediatric medical center. The marked differences which appear to be present in our current practice when compared to the experience at the same institution over twenty years ago have prompted a detailed look into this epidemiology. As anticipated, our current experience demonstrates clear trends which guide the formation of practice guidelines which are rational to implement in light of this data. Future prospective work will be necessary to study the success of implementation of these evidence based guidelines as well as to ascertain their merit in terms of beneficial clinical outcomes.

CHAPTER THREE
Deep Venous Thrombosis Associated with Musculoskeletal Infection in Children

BACKGROUND

Deep venous thrombosis (DVT) and pulmonary embolism are uncommon in children with an estimated incidence of less than 0.01%.[35] The use of intravenous catheters, trauma, surgery, and inherited coagulation disorders account for most of these events.[36]

Recent literature has demonstrated an association between deep musculoskeletal infections in children and the development of DVT and septic pulmonary embolism (SPE) as part of a life-threatening clinical syndrome of disseminated staphylococcal disease.[37-42] The emergence of community-acquired (CA) methicillin-resistant *S aureus* (MRSA) as a leading infectious organism in children has been concurrent with an increase in the frequency of DVT and SPE in musculoskeletal infection. Up to six percent of children with osteomyelitis caused by MRSA have been reported to develop DVT.[37] Still, there have been few published cases of deep musculoskeletal infection and thrombosis. A recent study from Texas Children's Hospital (TCH) in Houston cited eight cases of osteomyelitis and DVT occurring at that institution between August 2001 and December 2004; this report nearly doubled the number of previously reported cases. [37]

There is value in discerning the few children who will develop complications of DVT and SPE from the larger number of children who experience deep musculoskeletal infection without such an occurrence. Unfortunately, hematologic values are often

normal in these children, indicating that a prothrombic tendency is not essential to the development of thrombosis in the setting of musculoskeletal sepsis.[39, 42, 47] Evidence does exist, however, that suggests that the presence of selected genes encoding certain virulence factors might explain the occurrence of deep venous thrombosis associated with *S aureus* infections.[37, 42, 47] A recent report noted that the Panton-Valentine leukocidin (pvl) gene was encoded in the strains of MRSA and MSSA isolated from all five children who developed DVT in their series of twenty eight children with musculoskeletal infection.[47] Regardless, there is currently no adequate explanation as to why children with serious musculoskeletal infection may have increased susceptibility to DVT and SPE.

The purpose of this chapter is to report the incidence of DVT and SPE among children treated for deep musculoskeletal infection at a tertiary pediatric medical center in the southwest United States. As described earlier, we retrospectively reviewed all 554 cases of deep musculoskeletal infection treated at Children's Medical Center of Dallas from the period between January 1, 2002 to December 31, 2004 in an effort to characterize the most likely clinical and laboratory presentation of children who are prone to develop DVT or SPE.

METHODS

Medical records of children who were evaluated and treated for infection involving the spine, pelvis, upper or lower extremities in the emergency room or inpatient hospital of the Children's Medical Center of Dallas were retrospectively reviewed from the period between January 1, 2002 and December 31, 2004. Multiple data fields were recorded

including: patient demographics, age at admission, date of symptom onset, primary musculoskeletal infection diagnosis, location of infection, temperature, radiographic studies and results, laboratory studies and results, culture results, dates of admission and discharge, surgical procedures performed, and complications.

Records of patients diagnosed with both deep musculoskeletal infection and deep venous thrombosis were screened for and subjected to further analysis. Numerous data fields were recorded in addition to those earlier described including: DVT location and method of diagnosis, lung imaging and occurrence of SPE, genetic predisposition to thrombosis, family history of thrombotic disorders, use of anticoagulants, use of intravascular filter, placement of central venous catheter, and length of hospitalization before DVT diagnosis.

Children with deep musculoskeletal infection and DVT were categorized with respect to primary musculoskeletal diagnosis and location of infection, demographics, family and genetic histories, location of thrombosed veins, evidence of septic pulmonary emboli, and therapeutic interventions. Lab values and culture results of this group of children were then compared to those of the cohort of 541 remaining children who were treated for deep musculoskeletal infection during the time period of the study. Statistical analyses were performed comparing those with and without DVT, using independent sample t-tests when comparing means and Fisher's exact test when comparing rates. A p-value of 0.05 or less was required for statistical significance.

RESULTS

Thirteen children with deep musculoskeletal infection and DVT were detected and treated between January 1, 2002 and December 31, 2004 (see Table 7). Nine of the thirteen (69%) were male. The mean age of the children with DVT was 10.3 years (range: 2.9-14 years). In comparison, the mean age of the children with infection who did not have DVT was 6.7 years (range: 0.05-18 years) (p=0.0019). The infectious organism identified in twelve of the thirteen cases (92.3%) was *S aureus* (see Table 7). Of these, eight infections (66.7%) were caused by methicillin-resistant *S aureus* (MRSA), and four (33.3%) were caused by methicillin-sensitive *S aureus* (MSSA). One additional patient had an infection caused by *Streptococcus milleri.* All infections were considered to be community acquired. In comparison, among the 541 children with deep musculoskeletal infection who did not develop DVT, *S aureus* was the causative organism in 265 (48.9%). Of these, 154 infections (58.1%) were caused by MRSA and 111 (41.9%) were caused by MSSA. Furthermore, of the 45 children in with osteomyelitis and cultures positive for MSSA, only 3 (6.7%) developed DVT. In comparison, of the 43 patients with osteomyelitis and cultures positive for MRSA, 8 developed DVT (18.6%).

Table 7. Comparison between children with and without associated DVT.

	DVT	NON-DVT
NUMBER OF PATIENTS	13	542
MEAN ESR (MM/H)	63.0	54.1
MEAN CRP (MG/DL)	15.9	6.9
MEAN WBC ($X10^9$/L)	10.8	13.1
MEAN TEMPERATURE (°C)	38	37.2

PERCENTAGE MALE	59.4	69.2
AVERAGE AGE	10.3	6.7
S. AUREUS AS CAUSE (%)	92.3	48.9
MRSA AS CAUSE (%)	61.5	28.4
NUMBER OF SURGICAL PROCEDURES PER PATIENT	2.3	1.0
LENGTH OF HOSPITAL STAY (D)	27.4	6.5
DAYS FROM ONSET OF SYMPTOMS TO ADMISSION	14.8	9.1

Mean values for ESR, CRP, WBC, and Temperature represent an average of the first values measured upon hospitalization.

The primary musculoskeletal diagnosis of eleven of the patients with DVT was osteomyelitis (see Table 8). One patient had a primary diagnosis of septic arthritis, and another patient had a primary diagnosis of pyomyositis. The location of infection was adjacent to the site of DVT in ten patients (77%). The most frequent locations for infection associated with DVT were the distal femur, proximal tibia and proximal femur (see Figure 2).

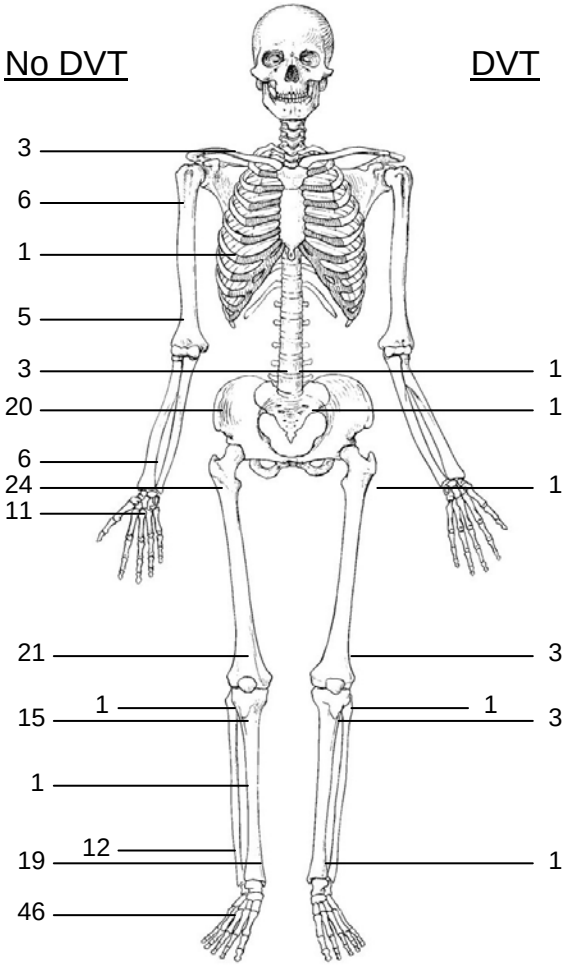


Figure 2. Foci of infection in osteomyelitis with and without associated DVT

The location of thrombosis was most frequently the femoral vein (six children), often extending into the popliteal vein (see Table 8). Thrombosis was found in the iliac veins of two children and in the vena cava of two additional children. The method of imaging employed when thrombosis was detected was evenly divided among MRI, computed tomography, and venous ultrasound with Doppler flow. Four thromboses were identified by each of these methods of imaging. One additional thrombosis was found using an echocardiogram. The majority of DVTs (8 out of 13; 61.5%) were recognized when imaging was employed to evaluate

the deep musculoskeletal infection (see Figure 3). Diagnosis of DVT was made an average of 3.1 days after admission (range: 0-8 days).

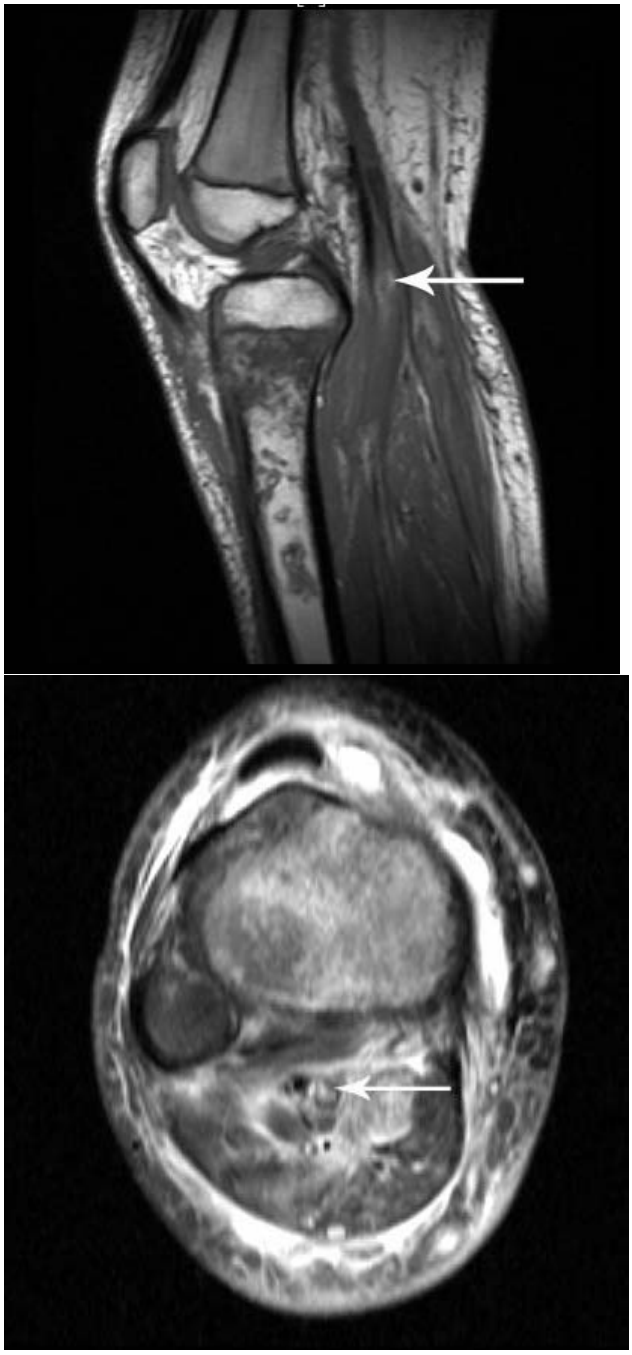


Figure 3. Sagittal and axial MRI images of proximal tibial osteomyelitis with DVT (arrows).

Pulmonary imaging revealed evidence of septic emboli in six of the thirteen children (46%) (see Table 8). One additional child had bilateral pneumonia and nodular opacities that may have been related to the SPE.

Risk factors which were assessed in this study included genetic predisposition for hypercoagulation, family history of blood disorders, and the use of central venous catheters (see Table 8). Of the nine children tested for genetic coagulation disorders, only two were found to be abnormal (heterozygous in both cases). One of these had a Prothrombin 20210A mutation, and the other had a Factor V Leiden mutation. Neither child had a family history of DVT or other hematologic problems. One additional child had several second degree relatives who had died from stroke, and another patient had a second degree relative who had died from an acute myocardial infarction at 53 years of age.

A central venous catheter was used in the treatment of twelve of the thirteen children who were found to have DVTs. However, the catheter was still present in only three of the children at the suspected time of onset of the thrombosis. In one child the DVT occurred adjacent to the area of infection and remote from the catheter location. In another child a DVT developed near the site of a femoral intravenous line. However, this child also had osteomyelitis in proximity to the thrombosis. In the remaining child, the thrombosis occurred near the site of the central venous catheter which was remote to the location of the musculoskeletal infection (patient 156 in Table 8).

Table 8 Clinical Characteristics of Children with Deep Musculoskeletal Infection and DVT

PATIENT	AGE (Y)	SEX	RACE	PRIMARY DX: LOCATION (ORGANISM)	VT LOCATION (MODE OF DISCOVERY)	PULMONARY FINDINGS	THROMBOTIC RISK FACTORS
32	13.5	M	B	O: RIGHT DISTAL TIBIA (MRSA)	SVC (ECHO)	CLEAR	NONE
84	13.8	M	H	O: RIGHT PROXIMAL FIBULA (MRSA)	RIGHT FEMORAL AND POPLITEAL VEINS (US)	CLEAR	CVC LEFT SUBCLAVIAN VEIN
128	9.0	M	B	O: RIGHT PROXIMAL TIBIA (MRSA)	RIGHT FEMORAL AND POPLITEAL VEINS (US)	SEPTIC EMBOLI	NONE
145	11.8	F	H	O: LEFT DISTAL FEMUR (MRSA)	LEFT FEMORAL AND POPLITEAL VEINS (US)	SEPTIC EMBOLI	NONE
156	12.0	M	H	O: RIGHT PROXIMAL TIBIA (MSSA)	SVC, LEFT INTERNAL JUGULAR AND SUBCLAVIAN VEINS (MRI)	CLEAR	CVC LEFT SUBCLAVIAN VEIN
348	10.6	F	W	O: LEFT SACRUM (MRSA)	LEFT COMMON, INTERNAL AND EXTERNAL ILIAC VEINS, RIGHT EXTERNAL ILIAC VEIN (CT)	BILATERAL NODULAR OPACITIES AND PLEURAL EFFUSIONS	HEART DISEASE IN GRANDFATHER AT AGE 53
368	13.7	F	W	O: RIGHT DISTAL FEMUR (MSSA)	RIGHT FEMORAL AND POPLITEAL VEINS (MRI)	INADEQUATE IMAGING	PROTHROMBIN GENE MUTATION 20210A
370	8.2	F	H	P: LEFT GASTROCNEMIUS (*S. MILLERI*)	LEFT POSTERIOR TIBIAL VEIN (MRI)	INADEQUATE IMAGING	NONE
434	7.9	M	W	O: THORACIC SPINE (MRSA)	AZYGOUS VEIN AND IVC (CT)	SEPTIC EMBOLI	NONE
445	10.3	M	W	O: RIGHT PROXIMAL FEMUR (MRSA)	RIGHT FEMORAL VEIN (US)	SEPTIC EMBOLI	CVC RIGHT FEMORAL VEIN
462	6.8	F	W	SA: LEFT HIP (MSSA)	RIGHT IJV, SIGMOID AND TRANSVERSE SINUSES (CT)	CLEAR	STROKES ON MATERNAL SIDE
496	2.9	M	B	O: RIGHT PROXIMAL TIBIA (MRSA)	RIGHT FEMORAL, EXTERNAL ILIAC, AND SAPHENOUS VEINS (CT)	SEPTIC EMBOLI	FACTOR V LEIDEN MUTATION
498	14.0	M	W	O: LEFT DISTAL FEMUR (MSSA)	LEFT POPLITEAL VEIN (MRI)	SEPTIC EMBOLI	NONE

M indicates male; F, female; B, black; H, Hispanic; W, white; O, osteomyelitis; P, non-tropical pyomyositis; SA, septic arthritis US, ultrasound with Doppler; CT, computed tomography; MRI, magnetic resonance imaging; CVC, central venous catheter.

Values for temperature, white blood cell count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were measured at the time of admission for the thirteen children with DVTs and compared to those of the children with deep musculoskeletal infection who did not develop this complication (see Table 7). The mean temperature at admission for children with DVT was 38.0°C compared with 37.2°C for those without DVT (p=.0704). The mean white blood cell count was 10.8 x 10^9/L in the DVT population versus 13.1 x 10^9/L for the remaining cohort. The mean ESR for children with DVT was 63.0 mm/h as compared to a mean ESR of 54.1 mm/h for the children without DVT. The differences between the DVT population and the remaining cohort for WBC and ESR values were not statistically significant. Finally, the mean CRP

for the DVT population was 15.9 mg/dL versus only 6.9 mg/dL for the children who did not develop DVT (p=0.0046).

Twelve of the thirteen children (92.3%) were treated with low molecular weight heparin (LMWH) after identification of the thrombosis. Anticoagulant therapy for two children was initiated with intravenous unfractionated heparin, but ultimately converted to LMWH in one child and warfarin in the other. One child was not treated with anticoagulants. One child had a Greenfield intravascular filter (Boston Scientific, Natick, MA) placed in the inferior vena cava to diminish pulmonary showering by septic emboli. Bacterial endocarditis developed in one child with disseminated infection. This child subsequently underwent tricuspid valvuloplasty for damage due to the bacterial endocarditis. Antibiotic treatment for musculoskeletal infection was not significantly altered by the finding of DVT in the subgroup of children in this study.

Surgical intervention for treatment of the underlying musculoskeletal infection was necessary 30 times for the thirteen children with DVT (2.3 procedures per child) versus 555 times for the 541 children without DVT (1.0 procedures per child) ($p<0.0001$) (see Table 1). The mean length of hospitalization for children with DVT was 27.4 days versus 6.5 days for children without DVT (p=0.0002).

Outpatient follow-up was conducted by orthopedic surgery, hematology, infectious disease, or the primary care physician. Documentation of resolution of the DVT was noted in the medical records of ten out of the thirteen children (76.9%) at an average of 9.2 weeks (range 40 to 140 days). There was inadequate follow up in three patients.

DISCUSSION

Deep venous thrombosis is rare in children and is most often related to the use of intravenous catheters, trauma, surgery, and inherited thrombotic risk factors.[35, 36] Several reports have also associated thrombosis and septic pulmonary emboli with deep musculoskeletal infection, including osteomyelitis and septic arthritis.[37,39,45] Despite these reports, the relationship between musculoskeletal infection and the incidence of DVT and SPE has been limited so as to make it difficult to characterize the children who are most likely to develop this complication. In this study, thirteen cases of DVT were found among 554 children with deep musculoskeletal infection treated at Children's Medical Center of Dallas from the time period between January 1, 2002 and December 31, 2004. The comparison of this subgroup of children to the larger cohort of children with deep musculoskeletal infection has revealed several characteristics which may be helpful in directing closer attention to those children who may be prone to this complication.

In general, children who developed DVT were older (10.3 yrs versus 6.7 yrs) than the remainder of children with deep musculoskeletal infection. There was a trend toward a higher incidence in males as opposed to females (69.2%). The locations of infection in the DVT population exclusively involved the spine, pelvis, and lower extremities with the majority occurring in the tibia (4 children) or femur (4 children). Children with DVT presented with considerably higher mean ESR and CRP levels (63.0mm/hr and 15.9mg/dL) than did the remaining children with deep musculoskeletal infection (54.1mm/hr and 6.9mg/dL).

Of the 206 children in the study with osteomyelitis as primary diagnosis, eleven developed DVT (5.2%). Lab cultures were positive for *Staphylococcus aureus* in all eleven children who had DVT associated with osteomyelitis. To the best of our knowledge, only 23 cases of *S aureus* osteomyelitis and concurrent thrombosis have been reported to the current date. [37-43, 45-46, 48] The two other thrombotic patients in our study had primary diagnoses of septic arthritis in one and pyomyositis in the other.

The strain of infectious organism may be associated with the development of DVT. A recent report from Texas Children's Hospital in Houston documented that, between August 2001 and December 31, 2004, 7 of 116 children (6.0%) treated for acute hematogenous osteomyelitis caused by MRSA developed DVT.[37] Our study demonstrated an even higher rate of DVT associated with MRSA osteomyelitis (18.6%) as compared with MSSA osteomyelitis (6.7%).

There is some evidence suggesting that the presence of the pvl gene encoded in strains of MRSA and MSSA may explain the occurrence of complications such as DVT associated with deep musculoskeletal infection.[44, 47] Of the eight children with osteomyelitis and DVT at TCH, seven exhibited the pvl gene in *S aureus* strain isolates.[37] A relationship between pvl-positive strains and other complications such as chronic osteomyelitis and prolonged hospitalization has also been noted.[47] In our retrospective review, the genetic makeup of cultured organisms was not determined. We hope to analyze this aspect of *S aureus* infection prospectively at our institution in the future.

Inherited prothrombotic disorders may have been involved in the development of DVT in two of the patients in our study. One patient was heterozygous for the Prothrombin gene mutation 20210A (patient 368) and another was heterozygous for a

Factor V Leiden mutation (patient 496). Two other patients may have carried slightly increased risk of thrombosis due to family histories of heart disease in a 53 year old grandfather (patient 348), and strokes on the maternal side (patient 462), respectively. However, there is not enough data to draw a useful conclusion given the small number of children in our series.

Thrombosis is well known as a complication of intravenous catheter use.[49] Two of the patients in our study developed DVT near the location of the catheter (see Table 8). In one of these patients, the musculoskeletal infection was also located at the site of DVT (patient 445). The presence of septic pulmonary emboli in the course of disease in this patient was more suggestive of DVT being related to infection rather than to catheter use alone. Only one child was noted to have a thrombosis near the site of the intravenous catheter (patient 156) but remote to the site of musculoskeletal infection. This child maintained clear lung fields on pulmonary imaging. We believe that this child's DVT was likely a complication of catheter use and probably unrelated to the infection..
Our study is consistent with previous reports of the association between deep musculoskeletal infection and the development of DVT and SPE in pediatric patients. A high index of suspicion should be maintained whenever an infection involves the pelvis or lower extremities, especially in an older child or adolescent who presents with markedly elevated CRP and ESR. Among the 554 cases reviewed in our study, 39 children were over nine years old at admission and had a primary diagnosis of osteomyelitis of the bones of the pelvis, thigh, or leg caused by *S aureus*. Nine of these children developed DVT (23.1%). Further concern should exist when MRSA is identified as the causative organism. There were 6 cases of DVT among the 19 children

(31.6%) in our study who were older than 9 at admission and had a primary diagnosis of osteomyelitis of the bones of the pelvis, thigh, or leg caused by MRSA. Under these circumstances, it is rational to request the radiologist's interpretation of the initial diagnostic MRI with respect to the possible presence of DVT. If inconclusive, then Doppler venous ultrasound or Magnetic Resonance Venography may be considered to evaluate for the possible presence of DVT. MRSA may have a unique propensity to cause DVT in association with musculoskeletal infection. Further study is necessary to evaluate potential bacterial and host genetic factors that may be responsible for the thrombotic tendency in these children. Physicians caring for osteomyelitis in areas where CA MRSA strains are common should be aware of this complication.

CHAPTER FOUR
Non-Tropical Pyomyositis

BACKGROUND

Pyomyositis is a bacterial infection of skeletal muscle occurring either spontaneously, as in primary pyomyositis, or secondary to penetrating injury or local spread from an adjacent infection. "Tropical pyomyositis," is frequently seen in many parts of Africa and the South Pacific, accounting for approximately 4% of surgical admissions in the tropical setting.[50, 51] "Non-tropical pyomyositis" is reported, albeit less commonly, in more temperate climates, where it occurs during the warmer months.[51-56] One study from southern Texas reported an incidence of 1 per 3,000 pediatric admissions.[52]

Pyomyositis is most common in the first and second decades of life with a slight male predominance of 2:1 to 3:1.[51, 57, 58] Single muscle involvement is typical; multiple sites were identified in only 16.6% of cases in a literature review of 676 patients which have been reported between 1960 and 2002.[59] The most common site of infection is the quadriceps, followed by the gluteal and iliopsoas muscles.[57]

Pyomyositis is thought to occur most typically as a result of the hematogenous bacterial seeding of skeletal muscle which has been predisposed to infection by the alteration of its normal defenses. Healthy skeletal muscle appears to be inherently resistant to infection, even in the face of bacteremia. Studies have been able to induce pyomyositis in laboratory animals via sublethal intravenous injection of *Staphylococcus aureus*, but only after muscles were traumatized by pinching, electric shock, or

ischemia.[60] Subclinical parasitic and viral infections have been proposed as precursors to tropical pyomyositis, but there does not appear to be a correlation between the geographic distribution of parasitic infections and pyomyositis.[57, 59] In the United States, non-tropical pyomyositis appears to be associated with immune compromise and impaired host bactericidal capabilities with case reports in patients who have diabetes, hematopoietic disorders, cancer, and HIV disease.[51, 58, 61]

Staphylococcus aureus is the most common pathogen involved in pyomyositis and has been reported in 50-85% of cases in the United States and in greater than 90% of cases in the tropics.[51,53,55,57,58,61,62] The second most common causative organism is Group A beta hemolytic Streptococcus (GABHS), which is reported in 25-50% of cases in the United States.[51, 63, 64, 54, 65] Other notable organisms which have been reported include E. coli (2.4%), Salmonella (1.5%), and M. tuberculosis (1.1%).[59]

Pyomyositis has been described as progressing through three distinct stages.[66] In the invasive stage, the causative organism enters the muscle through the circulation. A cascade of local inflammation develops which results in the insidious onset of diffuse muscle pain, general malaise, and low-grade fever.[59] Next, during the purulent stage, an abscess accumulates within the skeletal muscle and systemic signs and symptoms of infection begin to appear, including progressive pain, high fever, and swelling. This stage occurs approximately 10-21 days after the onset of symptoms and is identified as the cause of initial presentation for medical treatment in over 90% of children with pyomyositis.[57] Finally, in the late stage, the child presents with signs of systemic toxicity and septic shock, which may occur in up to 5% of children.[57]

Non-tropical pyomyositis is rare and often presents clinically with vague symptoms and an imprecise history. Infection is frequently located in muscles around the pelvis, creating diagnostic difficulty.[62, 67-75] Trauma to the affected muscle has been debated as a possible common etiological mechanism. Some authors have reported trauma as a preceding event in 39% to 60% of children in North America compared to the same occurrence in only 25% of children in the tropics.[57, 58, 61] Other reports have not substantiated this finding with a history of trauma solicited in <5% of reviewed cases.[59] Laboratory values and infectious indices often mirror those of other musculoskeletal infections. Until clinical signs and symptoms are more clearly quantified and delineated, pyomyositis will serve as a diagnostic challenge for physicians.

The purpose of this chapter is to report the incidence of pyomyositis among the 554 children with deep musculoskeletal infection in our retrospective review. Cases of pyomyositis will be analyzed and compared to the larger group of deep musculoskeletal infections.

METHODS

Medical records of children who were evaluated and treated for infection involving the spine, pelvis, upper or lower extremities in the emergency room or inpatient hospital of the Children's Medical Center of Dallas were retrospectively reviewed as discussed in Chapter Two. Records of children with a primary diagnosis of pyomyositis were screened for and subjected to further analysis. Numerous data fields were recorded in addition to those earlier described including: history of physiologic or metabolic

stressors that could affect bactericidal capability, presence of intramuscular abscess, and stage of pyomyositic infection.

Children with pyomyositis were categorized with respect to site and stage of infection, causative organism, demographics, method of diagnosis, and therapeutic interventions. Lab values and culture results of this group were compared to those of the cohort of 554 children who were treated for deep musculoskeletal infection during the time period of the study.

RESULTS

Twenty children with a primary diagnosis of pyomyositis were treated at Children's Medical Center of Dallas between January 1, 2002 and December 31, 2004 (Table 9). Eleven of these children were female (55%). The mean age of the children at admission was 6.8 years (range: 1.1–17.8 years). Fifteen of the 20 children (75%) were admitted to the hospital during the contiguous months of May through October. Ten children (50%) were admitted during the months of May and June alone.

Laboratory cultures were positive in 12 of the 20 cases (60%). The infectious organism identified in 8 of these cases was *S aureus* (66.7%). Four of the strains of *S aureus* were found to be methicillin resistant (50%). GABHS was identified as the causative organism in 2 of 12 (16.7%) positive cultures. The infectious organisms identified in the two other positive lab cultures were S*treptococcus milleri* and unidentified gram positive cocci.

Table 9. Clinical characteristics of children with non-tropical pyomyositis

Patient #	Age, y	Location of Infection	Organism	Abscess?	Diagnostic Imaging
25	10.7	L Leg (anterior and lateral compartments)	GABHS	No	None
111	1.2	R soleus and flexor hallucis longus	MSSA	No	MRI
112	3.2	L Iliopsoas, adductor and flexor musculature	No Growth	Yes	MRI
120	10.8	BL gastrocnemius and soleus, R peroneus longus and brevis	Gram Positive Cocci	No	MRI
121	1.1	R Hip	No Growth	No	MRI
140	14.2	R soleus	Staphylococcus aureus (coag. negative)	Yes	MRI
149	4.6	R subclavius and subscapularis	No Growth	Yes	MRI
227	4.2	L SCM	No Growth	No	CT
240	11.1	R adductor longus, obturator internus and externus	MSSA	No	MRI
244	2.3	L semimembranosus	MRSA	Yes	MRI
251	17.8	R iliopsoas	MRSA	Yes	CT/MRI
370	8.2	L Gastrocnemius	Streptococcus milleri	Yes	MRI
400	12.5	Muscles of R popliteal fossa	No Growth	No	MRI
437	8.1	R tensor fascia lata, vastus medialis and lateralis	No Growth	No	MRI
469	9.1	R semimembranosus	MRSA	Yes	MRI
483	4.1	R psoas major, tensor fascia lata, vastus lateralis, rectus femorus	No Cultures Sent	No	MRI
484	3	R extensor digitorum longus and soleus	No Growth	Yes	MRI
486	1.3	L triceps and L flexor forearm	GABHS	Yes	MRI
490	4.6	R flexor digitorum	MRSA	Yes	MRI
523	3.7	R flexor hallucis longus	MSSA	No	MRI

The site of infection was located in the pelvis or lower extremity in 16 of 20 (80%) children. Multiple muscles were involved in 11 cases (55%). The most commonly infected muscles were those of the posterior compartment of the leg, the quadriceps, and the iliopsoas (Table 9). Intramuscular abscesses were discovered in 11 of the 20 (55%) children. One child developed septicemia.

Methods of imaging employed in the evaluation of this group of children included radiography, ultrasound, bone scan, computed tomography, and magnetic resonance imaging. X-rays were normal in 14 of 15 patients (93.3%). Ultrasound results were normal in 9 of 11 cases (81.8%). Bone scan was negative in 4 of 5 (80%) of children on

which it was performed. CT was used to diagnose 1 of the 20 children with pyomyositis (5%). MRI was used in the evaluation of 18 children and was diagnostic in each case (Table 9).

Values for temperature, white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were measured at the time of admission for the twenty children with pyomyositis and compared to those of the 535 other children with deep musculoskeletal infection. The mean temperature at admission for children with pyomyositis was 37.5°C. The mean WBC was 12.9 x 10^9/L for this group, and the mean ESR and CRP were 53.2mm/h and 11.0mg/dL, respectively. The average length of time from onset of symptoms until admission was 4.3 days for children with a primary diagnosis of pyomyositis. Records of all children in the cohort were analyzed for histories of trauma, subjective fever, inability to bear weight, upper respiratory infection (URI), and pain. Of the 20 children diagnosed primarily with pyomyositis, 4 reported a history of trauma to the infected muscle (20%). Fifteen of the children with pyomyositis reported a fever (75%), and 8 reported an inability to bear weight upon the infected limb (40%). Three of the 20 children (15%) had a history of URI, and 18 reported pain at the site of infection (90%).

Medical records of each child were also examined for history of metabolic of physiologic stressors that could potentially cause immunocompromise. One child reported a recent history of intense exercise (patient 400). Another child (patient 25) was heterozygous for beta thalassemia, and an additional child (patient 121) had systemic lupus erythematosus (SLE). One of the children had a history of diabetes and

craniopharyngioma with pituitary removal (patient 140), and another (patient 251) had Crohn's disease.

Therapeutic interventions for children with pyomyositis included appropriate antibiotic therapy and surgical drainage of abscesses. All 11 children with abscesses were treated with at least one incision and drainage procedure in order to remove purulent material. Two patients underwent two surgeries, one patient underwent three surgeries, and one other patient underwent five surgeries. The average length of hospital stay for children with pyomyositis was 5.0 days. The only complication noted was the development of deep venous thrombosis (DVT) near the location of infection in one patient. The DVT resolved spontaneously after treatment with anticoagulants.

Outpatient follow-up was conducted by orthopedic surgery, pediatric surgery, or the primary care physician. Documentation of continued healing was noted in the medical records of each of the 13 children followed at Children's Medical Center of Dallas.

DISCUSSION

Pyomyositis accounts for approximately 4% of surgical admissions in the tropics, but is a rare disorder in more temperate climates.[50, 51] One study from southern Texas reported an incidence of 1 case of non-tropical pyomyositis per 3,000 pediatric admissions.[52] A retrospective review from North Carolina described a total of 18 patients presenting with primary pyomyositis over an eighteen year period.[53] In our review of 554 children with deep musculoskeletal infection who presented to Children's Medical Center of Dallas

between January 1, 2002 and December 31, 2004, there were 20 children diagnosed primarily with non-tropical pyomyositis.

Pyomyositis has been reported as occurring more frequently in temperate climates during the warmer months of the year.[51-56] Our study supports this seasonal distribution of infections. Fifteen of the twenty children in our study (75%) were admitted to the hospital during the contiguous months May through October; these are the six warmest months of the year in Dallas, Texas. Ten children (50%) were admitted during the months of May and June alone. Children with pyomyositis presented with mean ESR and CRP levels (53.2mm/hr and 11.0 mg/dL) similar to those of the remaining children with deep musculoskeletal infection (55.4 mm/hr and 8.3 mg/dL), underscoring the need for appropriate imaging studies to identify primary muscular foci of infection.

Previous publications regarding pyomyositis have reported a male predominance of 2:1 to 3:1. [51, 57, 58] There was a more even distribution of pyomyositis by gender in our study, as 11 of the 20 patients (55%) were female.

The most common causative organism in pyomyositis is *Staphylococcus aureus*, with 50-85% of cases in the United States and greater than 90% of cases in the tropics attributed to this pathogen.[51, 53, 55, 57, 58, 61, 62] Eight of the 12 positive lab cultures (66.7%) in our review identified *S. aureus* as the infectious organism. Four of these pathogens were identified as methicillin resistant *S aureus* (MRSA). The second most common causative organism is Group A beta hemolytic Streptococcus (GABHS), which is reported in 25-50% of cases in the United States.[51-55, 64-65] In our study, GABHS was the second most common organism; it was identified in 2 of 12 (16.7%) positive cultures.

Single muscle involvement is typical with pyomyositis. Multiple sites of infection were identified in only 16.6% of cases in a literature review of 676 patients that have been reported between 1960 and 2002.[59] The most common foci is the quadriceps, followed by the gluteal and iliopsoas muscles.[57] In our study, multiple muscles were infected much more commonly. Eleven of the 20 patients reviewed (55%) had more than one site of pyomyositis. The primary foci of infection was in the pelvis or lower extremity in 16 of 20 (80%) children, with the quadriceps, iliopsoas, and muscles of the posterior compartment of the leg most commonly affected.

Trauma to the affected muscle has been proposed as a possible etiological mechanism, with some authors reporting trauma as a preceding event in 39% to 60% of children with pyomyositis in North America.[,57, 58, 61] Other reports have not substantiated this finding with a history of trauma solicited in <5% of reviewed cases.[59] Trauma to the affected muscle was present in the history of 4 of the 20 (20%) children in our study. One of the children in this group (patient 370) had a toothpick lodged in the gastrocnemius for approximately two months before muscular infection occurred. Two children received blunt trauma within one week previous to the time of hospital admission (patients 484 and 486). One other child received an intramuscular injection near the site of pyomyositis one day previous to admission (patient 149).

Non-tropical pyomyositis is described as progressing through three distinct stages (invasive, purulent, late) beginning with diffuse pain and continuing to focal abscess formation and finally to septicemia.[59, 66] The invasive stage has been described as the most diagnostically challenging, due to the absence of both systemic signs of infection and local inflammation.[59] According to one study, the purulent stage occurs between 10-

21 days after the onset of symptoms and is the stage of initial presentation for over 90% of children with pyomyositis.[57] In our study, far more children (8 of 20; 40%) presented in the invasive stage than expected, and children entered the purulent stage, on average, much sooner after the onset of symptoms (3.9 days) than previously reported. The single child in our review with septicemia (patient 486) first developed symptoms only 6 days before blood cultures became positive. These data emphasize the need for improved diagnostic criteria for pediatric pyomyositis.

This chapter provides the first major reporting on the increasing incidence of non-tropical pyomyositis in children in the southwest United States. It is expected that pyomyositis will be encountered more frequently at our institution in the future, especially during the warmer months of the year. Further consideration of the evaluation and treatment of this disorder is certainly warranted. We hope to incorporate satisfactory methods of handling non-tropical pyomyositis into our clinical practice guidelines for deep musculoskeletal infections in children; we plan to assess this new treatment algorithm in a future prospective study.

CHAPTER FIVE
Conclusions and Recommendations

THE EPIDEMIOLOGY AND MANAGEMENT OF DEEP MUSCULOSKELETAL INFECTIONS HAVE CHANGED SIGNIFICANTLY AT CHILDREN'S MEDICAL CENTER OF DALLAS OVER THE LAST 50 YEARS

In 1982, Jackson and Nelson reported a retrospective review of the epidemiology of bone and joint infections seen at Children's Medical Center of Dallas (CMC) and Parkland Memorial Hospital.[11] The identified 471 cases of septic arthritis over 26 years (18.1 per year), and 259 cases of osteomyelitis over 22 years (11.7 per year) and found that Staphylococcus aureus was the most common causative organism.[11]

Between January 1, 2002 and December 31, 2004, we performed a retrospective review of the children who were treated for musculoskeletal infection at CMC. At that time our clinical perception led us to believe that there had been a marked change in the local epidemiology of musculoskeletal infection. We identified 554 cases of deep infection, including: 212 children with osteomyelitis (71 per year), 118 with septic arthritis (39 per year), 204 children with deep abscesses requiring operative drainage (69 per year), and 20 children with primary pyomyositis (6.7 per year). According to the United States Census Board, the average population of a six county region, from which 97.6% of the children with infection were referred, grew from 1,687,122 to 3,651,037 (a 2.2 fold increase) between the comparative time periods of the two studies. While population growth may help explain the increase in children with septic arthritis, which

grew by a similar magnitude, it does not explain the rate of growth of children with osteomyelitis (a 6 fold increase) or the newly reported cases of pyomyositis.

Our retrospective research led to several observations about the process of evaluation and treatment of musculoskeletal infection at a tertiary pediatric medical center. Specifically, we quantified the type and amount of resources committed to the care of this growing patient population. The 554 children with deep musculoskeletal infections were hospitalized a total of 591 times. The average length of hospitalization was 11 days for children with osteomyelitis, 8 days for children with pyomyositis, 6.4 days for children with septic arthritis, and 3.6 days for children with abscess. In total, there were 4298 hospital days that were related to musculoskeletal infection during the three year period (1433 hospital days per year). A variety of hospital resources were utilized in the evaluation and treatment of these children, including: 1690 radiology procedures, 2536 cultures sent, 766 consultations, and 455 surgical procedures.

Another notable finding of our review was the wide array of antibiotics which were utilized during the treatment course and the high frequency with which changes in antibiotic type, dosing, frequency, and duration were made by treating physicians. Over 31 different antibiotics were used in treating the children with osteomyelitis.

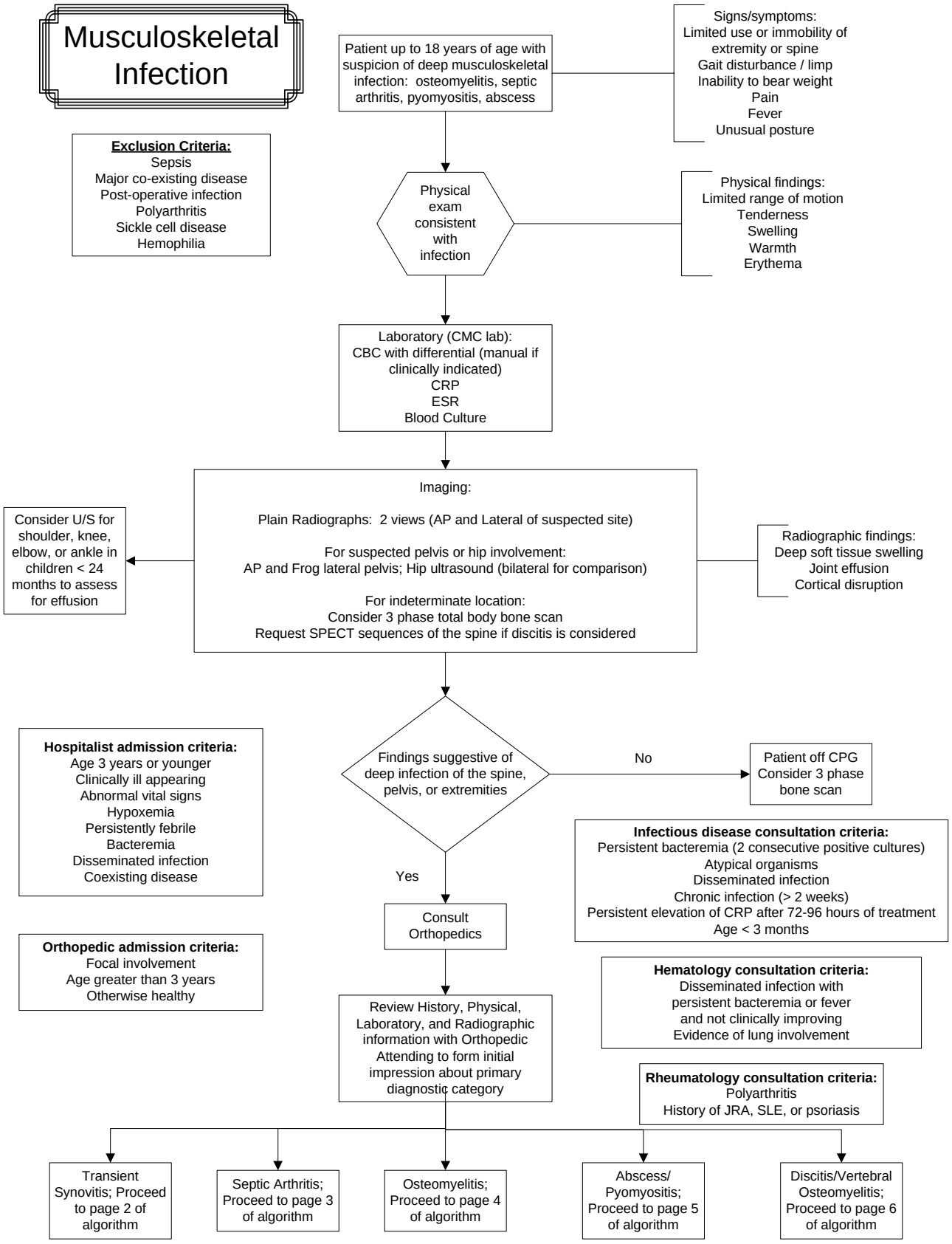
RATIONAL DEVELOPMENT OF CLINICAL PRACTICE GUIDELINES

Given the findings described above, we were compelled to assemble a multi-disciplinary team in an effort to review the retrospective experience and develop a set of evidence-based treatment guidelines so as to standardize patient care for children with musculoskeletal infection at CMC (figure 4). Previous research at Children's Hospital,

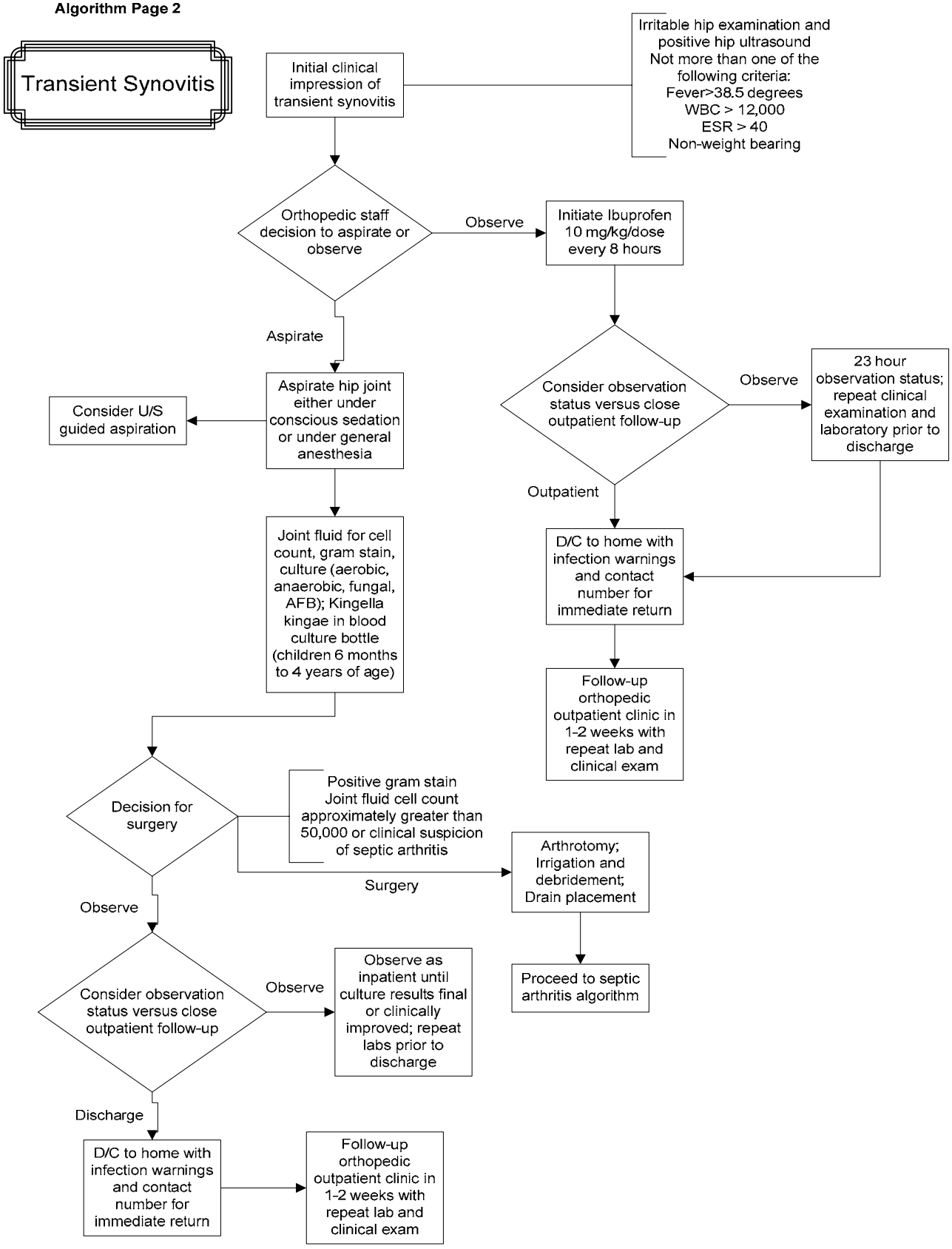
Boston has shown that the development of clinical practice guidelines by an interdisciplinary group resulted in a significantly higher rate of performance of initial and follow-up C-reactive protein tests, lower rate of initial bone scanning, lower rate of presumptive surgical drainage, greater compliance with recommended antibiotic therapy, faster change to oral antibiotics, and shorter hospital stay (from 8.3 to 4.8 days) when comparison was made to a retrospectively reviewed cohort of children who were not treated according to the guidelines [17.]

Our guideline for the evaluation and treatment of musculoskeletal infection (figure 4) begins with the initial clinical appraisal of a child with a possible infection, and then outlines thought and decision-making pathways based on conclusions drawn from appropriate labs, imaging modalities, and clinical acumen. A multi-disciplinary perspective is achieved through the inclusion of other specialties besides orthopedics, such as pediatric medicine, infectious disease, pediatric surgery, rheumatology, hematology-oncology, emergency room, operating room, nursing, laboratory, radiology, social work, physical therapy, and pharmacy.

Our goal is to initiate the guidelines, prospectively study a cohort of children who are treated by the guidelines, and make comparison to clinical outcomes of the retrospective cohort. We believe that appropriate use of the guidelines will result in greater compliance with recommended antibiotic therapy, lower rate of bone scanning, fewer surgical procedures, faster change to oral antibiotics, and shorter hospital stays. We do, however, anticipate a higher rate of MRI scanning.

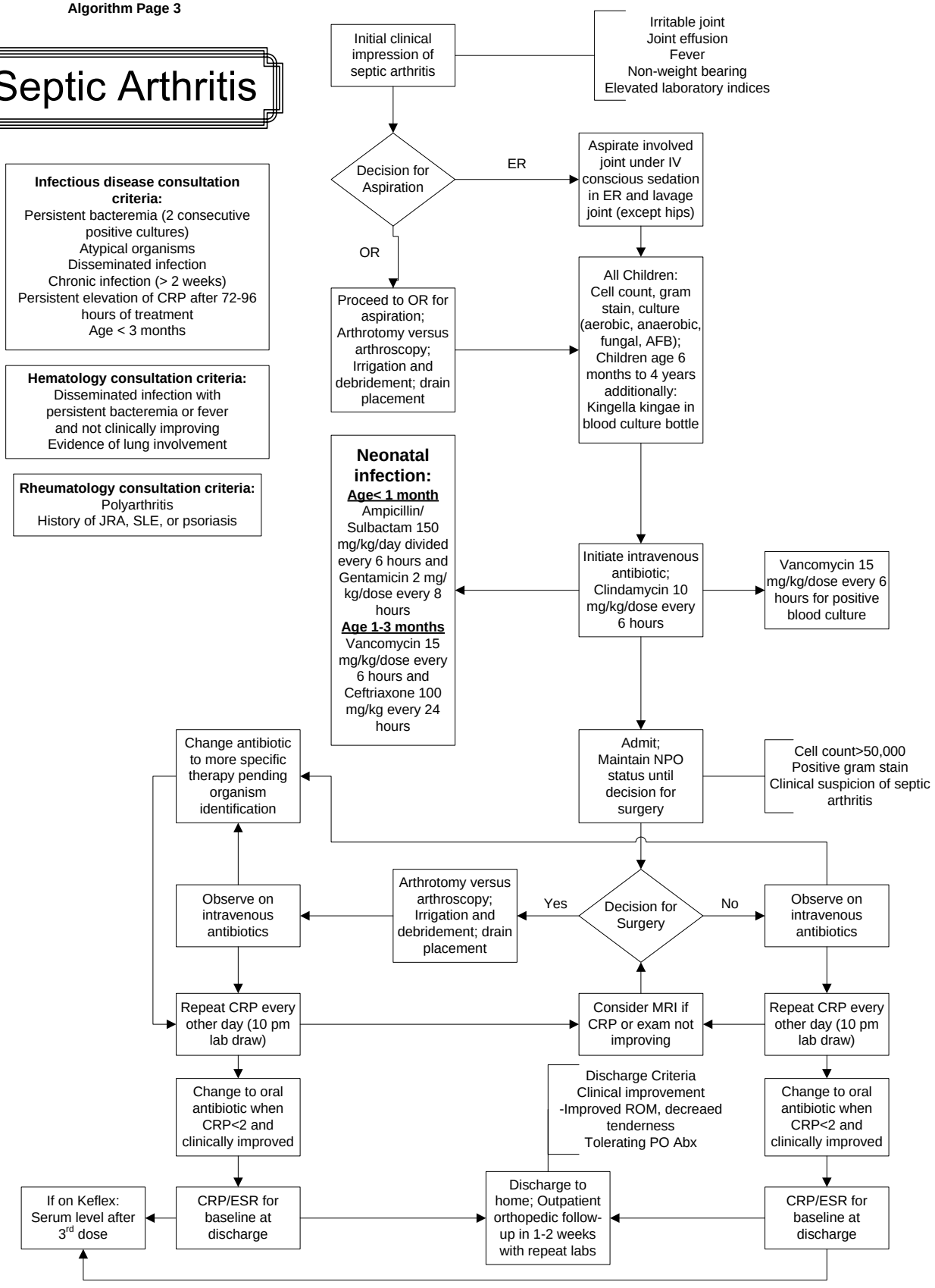

Musculoskeletal Infection
Patient up to 18 years of age with suspicion of deep musculoskeletal infection: osteomyelitis, septic arthritis, pyomyositis, abscess
Signs/symptoms:
Limited use or immobility of extremity or spine
Gait disturbance / limp
Inability to bear weight
Pain
Fever
Unusual posture
Exclusion Criteria:
Sepsis
Major co-existing disease
Post-operative infection
Polyarthritis
Sickle cell disease
Hemophilia
Physical exam consistent with infection
Physical findings:
Limited range of motion
Tenderness
Swelling
Warmth
Erythema
Laboratory (CMC lab):
CBC with differential (manual if clinically indicated)
CRP
ESR
Blood Culture
Imaging:
Plain Radiographs: 2 views (AP and Lateral of suspected site)
For suspected pelvis or hip involvement:
AP and Frog lateral pelvis; Hip ultrasound (bilateral for comparison)
For indeterminate location:
Consider 3 phase total body bone scan
Request SPECT sequences of the spine if discitis is considered
Consider U/S for shoulder, knee, elbow, or ankle in children < 24 months to assess for effusion
Radiographic findings:
Deep soft tissue swelling
Joint effusion
Cortical disruption
Findings suggestive of deep infection of the spine, pelvis, or extremities
No
Patient off CPG
Consider 3 phase bone scan
Yes
Hospitalist admission criteria:
Age 3 years or younger
Clinically ill appearing
Abnormal vital signs
Hypoxemia
Persistently febrile
Bacteremia
Disseminated infection
Coexisting disease
Infectious disease consultation criteria:
Persistent bacteremia (2 consecutive positive cultures)
Atypical organisms
Disseminated infection
Chronic infection (> 2 weeks)
Persistent elevation of CRP after 72-96 hours of treatment
Age < 3 months
Consult Orthopedics
Orthopedic admission criteria:
Focal involvement
Age greater than 3 years
Otherwise healthy
Hematology consultation criteria:
Disseminated infection with persistent bacteremia or fever and not clinically improving
Evidence of lung involvement
Review History, Physical, Laboratory, and Radiographic information with Orthopedic Attending to form initial impression about primary diagnostic category
Rheumatology consultation criteria:
Polyarthritis
History of JRA, SLE, or psoriasis
Transient Synovitis; Proceed to page 2 of algorithm
Septic Arthritis; Proceed to page 3 of algorithm
Osteomyelitis; Proceed to page 4 of algorithm
Abscess/ Pyomyositis; Proceed to page 5 of algorithm
Discitis/Vertebral Osteomyelitis; Proceed to page 6 of algorithm

Algorithm Page 2

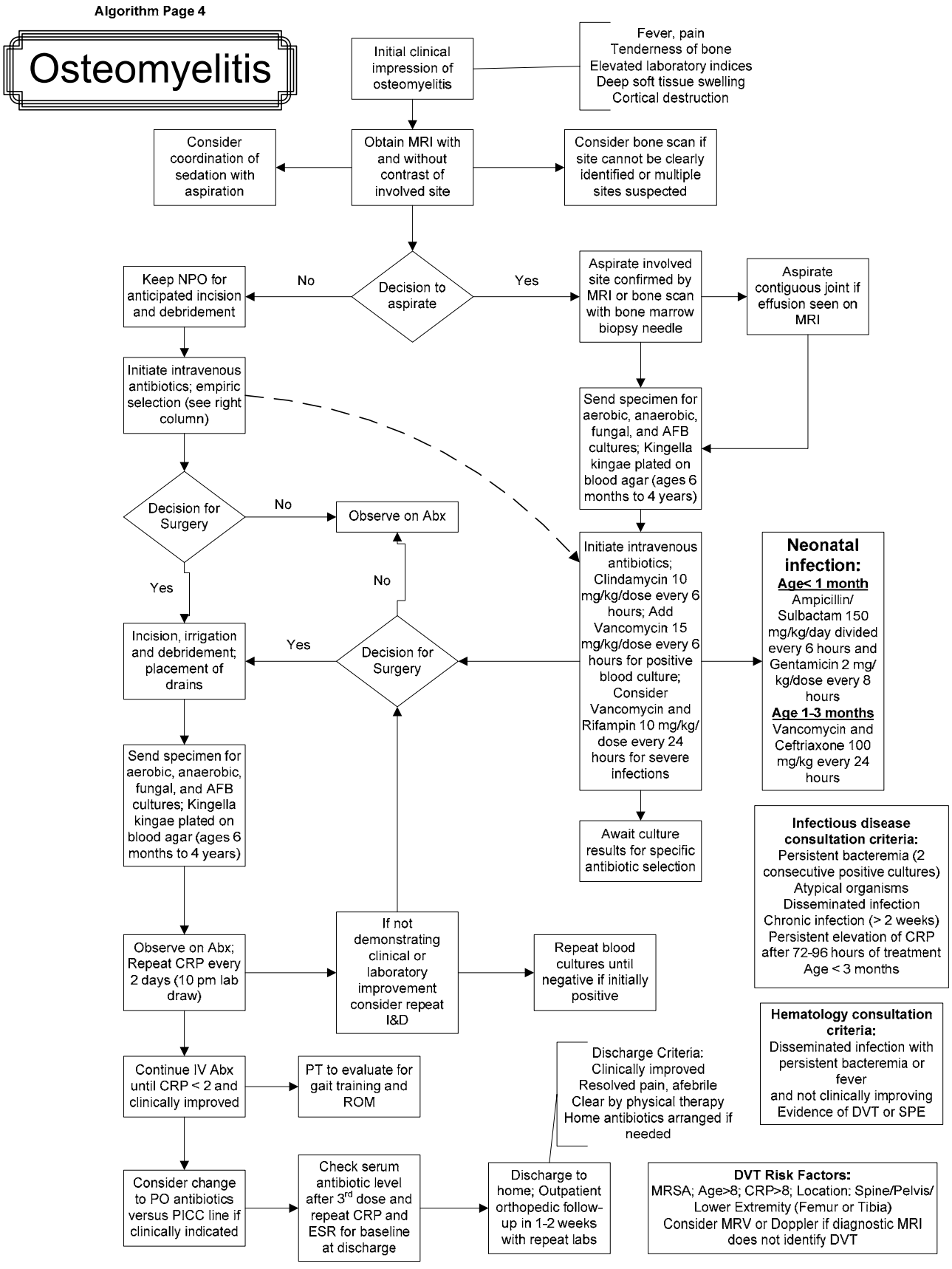


Algorithm Page 3

Septic Arthritis

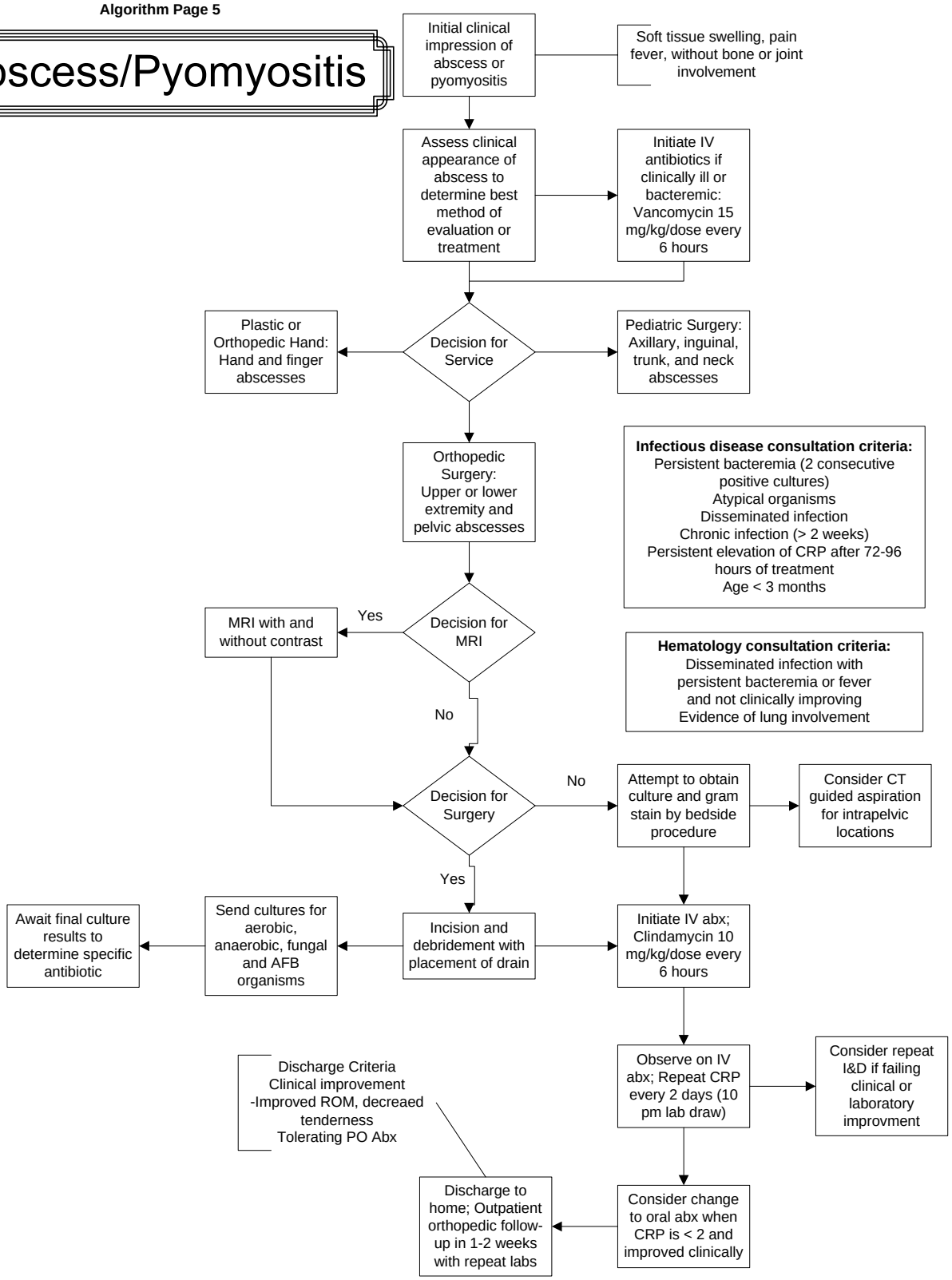


Algorithm Page 4



Algorithm Page 5

Abscess/Pyomyositis



Algorithm Page 6

Discitis/Vertebral Osteomyelitis

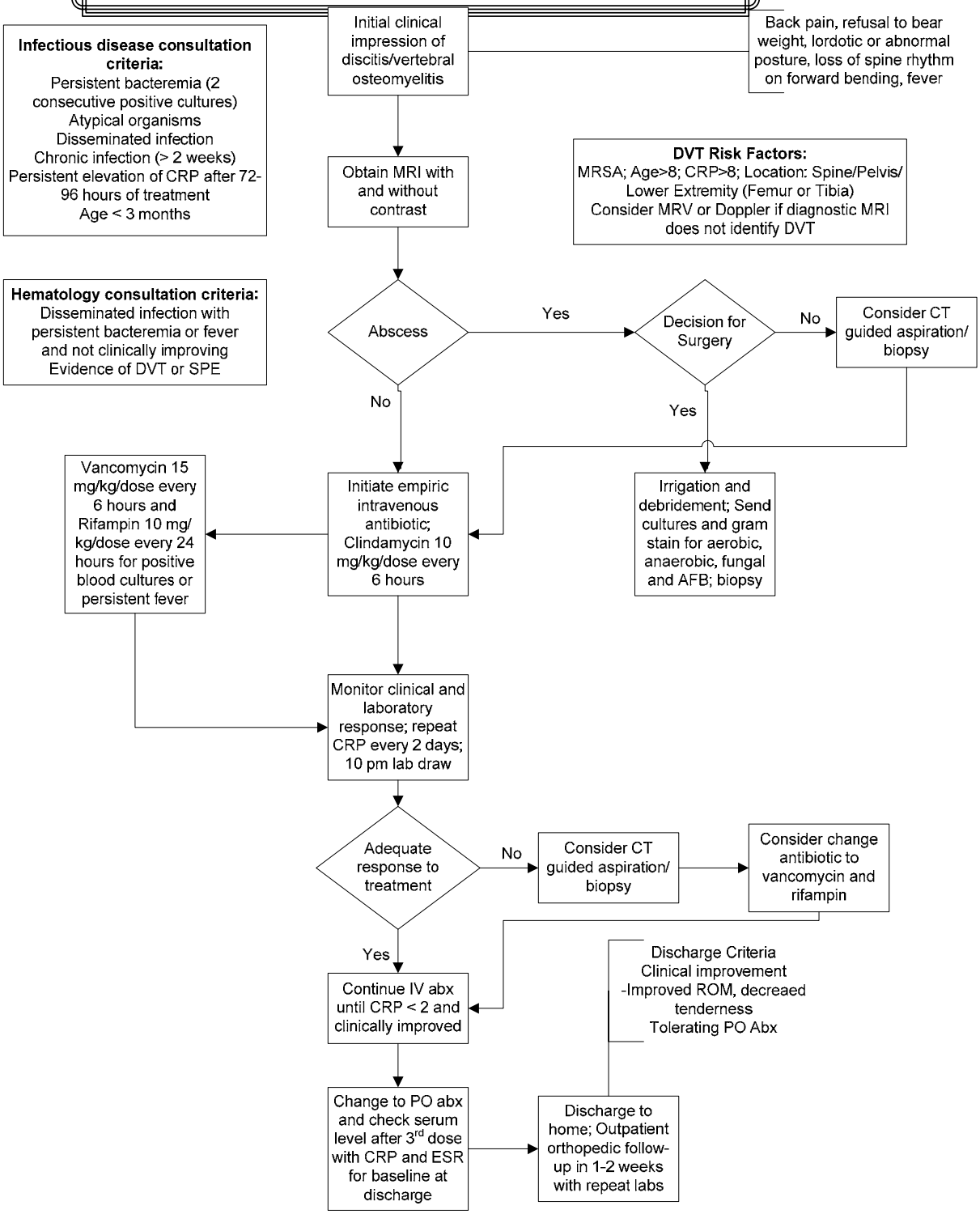


Figure 4. Proposed guideline for the evaluation and treatment of musculoskeletal infection.

CHILDREN WITH DEEP MUSCULOSKELETAL INFECTION THAT ARE PRONE TO DEVELOP DVT AND SPE HAVE CERTAIN RECOGNIZABLE CLINICAL CHARACTERISTICS

In our retrospective review, thirteen cases of DVT were found among 554 children with deep musculoskeletal infection treated at CMC from the time period between January 1, 2001 and December 31, 2004. The population of children who developed thromboses were compared to the 541 children who did not. The goal was to identify clinical criteria help the clinician discern those children prone to develop DVT in the general pediatric patient population with deep musculoskeletal infection.

In general, children who developed DVT were older (10.3 yrs versus 6.7 yrs) than the remainder of children with deep musculoskeletal infection. Eleven of the thirteen deep venous thromboses occurred in children with osteomyelitis (84.6%), while only 201 of the 541 children without DVT (37.1%) were diagnosed with osteomyelitis. *S aureus* was determined to be the causative organism in 12 of the 13 cases (92.3%) of deep musculoskeletal infection complicated by DVT. *S aureus* was cultured in only 265 of 542 (48.9%) of the patients who did not develop thrombosis. The locations of infection in the DVT population exclusively involved the spine, pelvis, and lower extremities with the majority occurring in the tibia (4 children) or femur (4 children). Children with DVT presented with higher mean CRP levels (15.9mg/dL) than did the remaining children

without DVT (6.9mg/dL). These findings, along with the increased surgical procedures per child (2.3 versus 1.0 cases) and the longer length of hospitalization in children with DVT (27.4 versus 6.5 days) support the conclusion that these children have a more advance degree of infection at the time of admission when compared to children without DVT.

A high index of suspicion should be maintained whenever osteomyelitis is caused by *S aureus*, and involves the spine, pelvis, or lower extremities, especially in an older child or adolescent who presents with markedly elevated CRP. Under these circumstances, it is rational to request the radiologist's interpretation of the initial diagnostic MRI with respect to the possible presence of DVT. If inconclusive, then Doppler venous ultrasound or Magnetic Resonance Venography may be considered to evaluate for the possible presence of DVT. We plan on evaluating this diagnostic guideline prospectively.

Future studies should address the possible association between deep musculoskeletal infection and the development of DVT and SPE at the molecular level in addition to the clinical one. Recently, evidence has been published that implicates the Panton-Valentine leukocidin (pvl) gene as a virulence factor in *S aureus* strains that infect patients who eventually develop DVT.[35] We hope to analyze this aspect of *S aureus* infection at our institution in the future.

NON-TROPICAL PYOMYOSITIS IS A MAJOR PRIMARY FORM OF DEEP MUSCULOSKELETAL INFECTION IN CHILDREN

In our review of 554 children with deep musculoskeletal infection who presented to Children's Medical Center of Dallas between January 1, 2002 and December 31, 2004, there were 20 children diagnosed primarily with non-tropical pyomyositis. Although several recent reports have identified an increasing incidence of pyomyositis in the United States, chapter four provides the first major reporting on non-tropical pyomyositis in children in the southwest United States.[36-41] It is expected that pyomyositis will be encountered more frequently at our institution in the future, especially during the warmer months of the year. Further consideration of the evaluation and treatment of this disorder is certainly warranted. We hope to incorporate satisfactory methods of handling non-tropical pyomyositis into our clinical practice guidelines for deep musculoskeletal infections in children, and we plan to assess this new treatment algorithm in a future prospective study.

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