Pediatric Musculoskeletal Infection An Update Through the Four Pillars of Clinical Care and Immunothrombotic Similarities With COVID-19

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Abstract: Due to the potential for devastating complications, few conditions in pediatric orthopaedics provoke more apprehension than a child with a musculoskeletal infection (MSKI). The infectious organisms, technology to diagnose MSKIs, and the pharmacology to treat MSKIs are evolving continuously. For these reasons, it is essential that pediatric orthopaedic surgeons be up to date on the current and future MSKI practices. In this review, current and future practices are systematically reviewed and categorized by the four main tasks the care team treating MSKI must complete: 1) Determine the location of the potential infection, 2) Determine if it is an infection, and if so, what is the organism? 3) Determine how severe the infection is, and 4) Determine how to treat the infection? Considering current events, the philosophy and tools highlighted for use in MSKI are paralleled in COVID-19 (SARS-CoV-2).

Key Concepts:

- In the setting of infection, be certain to evaluate the bone, muscle, and intra-articular space with a rigorous physical exam and MRI since multifocal infection are common in children over the age of four.
- If cultures can be obtained within 24 hours, do not hold antibiotics.
- Trending plasma and cellular acute phase measures are useful in determining if an infection is worsening or improving, while peak values prognosticate poor outcomes in patients with MSKI, especially thrombotic pathology.
- Pharmacologics are needed to eradicate the MSKI and to combat the exuberant acute phase response (APR). Together, these measures can limit the consequences of sepsis induced coagulopathy (SIC) and systemic inflammatory response syndrome (SIRS).
- There are reciprocal lessons to be learned from treating patients with MSKI and those with COVID-19. Both provoke a complex APR that can be considered immunothrombotic, involving both the inflammatory and coagulation elements of the "survival" APR.

Introduction

Pediatric orthopaedic surgeons are frequently called upon to evaluate children with suspected MSKI. For example, the Children's Orthopaedic Trauma and Infection Consortium for Evidence based Studies

(CORTICES) group determined that pediatric MSKI accounts for nearly 1 in 10 orthopaedic consultations at academic pediatric tertiary care centers. Fortunately, modern medicine has dramatically reduced the mortality

Conventional Wisdom:	"The sun never sets on a septic hip."	Task 1
Old Tools:	Physical examX-rayUltrasound	
Shortcoming of Old Tools:	 Anatomic ascertainment bias – focus on intra-articular processes Culturing and debriding aseptic tissue 	
New Wisdom:	 Intra- and extra-articular tissues are targets of common bugs Bone, muscle, and/or the intra-articular space may be infected Over the age of 4, local and distant dissemination is common 	
New Tools:	Rigorous physical examFast-sequence MRISharpie marker	

of MSKI in children, which was estimated as high as 40% in the pre-antibiotic era.^{2, 3} Although few pediatric patients succumb to MSKI in the U.S., it continues to cause significant morbidity in children through long-term negative impacts on the growing skeleton.⁴⁻⁷ Thus, it is essential that pediatric orthopaedic surgeons be armed with the best tools to provide efficient and accurate workup and up-to-date knowledge of the optimal treatment for each organism they encounter.

Paramount to caring for these children, there are four tasks that all members of the medical and surgical team should set out to complete in cases of suspected MSKI. The team should determine: 1) Where is the infection? 2) Is it an infection and if so, what is the pathogen? 3) How severe is the infection? 4) How to treat the infection? Given the heterogeneity of MSKI from one institution to another, it is beneficial to understand the philosophy and tools of these tasks to maximize the benefit to the child. In this review, the tools to accomplish these four tasks will be discussed, highlighting current best practices and recent advancements. Interestingly, MSKI and COVID-19 share similarities, such that each provokes a complex acute phase response that can be considered immunothrombotic involving both the inflammatory and coagulation elements of the "survival" APR;

therefore, this review will highlight reciprocal lessons to be learned from treating patients with MSKI and patients with COVID-19.

Task 1: Where Is the Infection?

Focus on the Joints First

The developing musculoskeletal system within children is an ideal target for bacteria for a multitude of reasons. Bacteria, like mesenchymal stem cells or cancers, have a tropism for the microenvironment of damaged and regenerating tissue.^{8,9} Molecularly, growing bone and muscle mimic regenerative tissue, predisposing it to similar relative risk of being targeted by bacteria. Specifically, bacteria express virulence factors with lock and key mechanisms that can directly interact with factors expressed by regenerative or growing muscle and bone. Additionally, unique characteristics of the physis, such as robust 'tortuous' vascularity¹⁰ and its relative immune privileged nature, 11 can likewise predispose this site to initiation of infection. Together, these molecular factors support the long-standing observation that developing children are susceptible to 'spontaneous' infections, predominately at or around major joints. For reasons not completely understood, lower extremities are far more susceptible to spontaneous MSKI than upper extremities, with the femur (hip and knee) being the most susceptible.

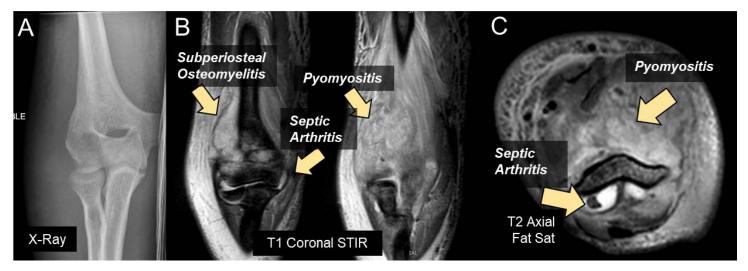


Figure 1: Advantages of Fast-Sequence MRI over X-ray and Ultrasound. A 16-year-old presented with a painful elbow joint. X-ray (A) did not reveal diagnostic information and ultrasound (not shown) was suggestive of a septic joint. The elbow fast-sequence MRI was performed non-sedated in less than 15 minutes which revealed invaluable diagnostic information for culture and debridement: B) MRI (T1 Coronal STIR sequence) and C) (Axial T2 Fat-Sat) illustrate evidence of simultaneous subperiosteal osteomyelitis, septic arthritis, and pyomyositis. Without this information, culture and surgical debridement would have been primarily focused on the intra-articular space and potentially intra-osseous, whereas the primary focus of the infection was extra-articular in the muscle and sub-periosteal space. (Figure permission: Schoenecker Laboratory)

Joint Pain is Not Always Septic Arthritis— Investigate 3-Dimensionally

Armed with the understanding that bacteria target developing musculoskeletal tissue, the most important goal of the medical and surgical team is to quickly determine which tissues and/or joint(s) are involved. In the past, an irritable joint with other diagnostic criteria suggesting MSKI was assumed to be an intra-articular process—septic arthritis. So much so that the popular moniker, "The sun never sets on a septic hip," is still often taught to medical trainees. Although time does matter in outcomes of pediatric MSKI, precise knowledge of what tissue is infected is essential to debride and culture the infected tissue. As such, MRI has become a practical tool in the arsenal of MSKI workup.

Prior to MRI, most cases of an antalgic joint were assumed to be isolated (Figure 1). This led to a one-dimensional, and therefore limited, understanding of this disease process. In current practice, fast sequencing MRI (Table 1), which can be done in non-sedated children, has significantly changed our understanding

into a three-dimensional evaluation consisting of the intra-articular space, bone, and muscle (Figure 1). For example, just one decade ago, pericapsular hip pyomyositis was considered a tropical infection; however, now it is a common diagnosis in temperate climates. 12-16 At one center, by employing routine fast sequencing MRI, pericapsular hip pyomyositis was found to be twice as common as an isolated septic hip. 12 The distinction of this diagnosis is clinically relevant, as draining an aseptic hip with a sympathetic effusion is not only unnecessary, but also may potentially allow dissemination from the pyomyositis into the intra-articular space. Furthermore, routine use of MRI has similarly revealed heterogeneity of infectious pathologies around the knee with synovitis, isolated osteomyelitis, and bursitis occurring at a greater frequency than isolated septic arthritis.⁴ In order to best facilitate treatment for MSKIs, a sensitive and multidimensional assessment of muscle and bone is required; currently, this is best achieved through MRI.

	Table 1: Snapshot- Fast-Sequence MRI for Pediatric MSKI							
	Suspected Focus of Pathology	MSK Infection Screening Protocol	Initial Field of View	1st sequence	2nd sequence	3rd sequence	4th sequence	Estimated Time (min)
	Pelvis	Pelvis	Iliac crest to mid femur	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
	Hip	Pelvis	Iliac crest to mid femur	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
	Femur	Femur	Hip joint to knee joint	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
dy	Knee	Knee	Mid femur to mid tibia	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
Lower Body	Tibia	Tibia	Knee joint to Ankle joint	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
Lo	Ankle	Ankle & Foot	Mid tibia to toes / plantar foot	Coronal STIR	Coronal T1	Axial T2 fat sat	Sagittal STIR	12-18
	Foot	Ankle & Foot	Mid tibia to toes / plantar foot	Coronal STIR	Coronal T1	Axial T2 fat sat	Sagittal STIR	12-18
	Linksows I F	Screening LE with	Iliac crest to plantar foot	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
	Unknown LE	CTLS spine	Occiput to coccyx	Sagittal STIR	Sagittal T1	Axial T2		10-15
Axial	Spine	CTLS spine	Occiput to coccyx	Sagittal STIR	Sagittal T1	Axial T2		
	Shoulder	Shoulder	Shoulder joint to mid humerus	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
	Humerus	Humerus	Shoulder joint to elbow joint	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
φ	Elbow	Elbow	Mid humerus to mid forearm	Coronal STIR	Coronal T1	Axial T2 fat sat	Sagittal STIR	12-18
Upper Body	Forearm	Forearm	Elbow joint to Wrist joint	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
g	Wrist	Wrist & Hand	Mid forearm to fingertips	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
	Finger	Hand	Wrist joint to fingertips	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15
	Unknown UE	Screening UE	Shoulder joint to fingertips	Coronal STIR	Coronal T1	Axial T2 fat sat		10-15

^{*}For the "Ankle & Foot" protocol, the imaging planes are in reference to the foot. ** For the "Unknown LE" focus of pathology, the "screening LE" protocol is done first; if negative, then the "CTLS" spine protocol is performed. UE= upper extremity and LE= lower extremity, CTLS = Cervical, Thoracic, Lumbar, Sacrum, Spine, STIR=Short TI Inversion Recovery

Conventional Wisdom:	"It takes days to get cultures and sensitivities."	Task 2
Old Tools:	Bacterial culture media	
Shortcoming of Old Tools:	Century old culturing techniquesAnatomic ascertainment bias	
New Wisdom:	 Tests that do not rely on bacterial growth High throughput genomic and proteomic analysis Fast-sequence MRI to direct cultures 	
New Tools:	 PCR-based amplification of bacterial DNA (now) 'Omics' based analysis (future) 	

5

The Best Hands Should Be Hands On

Even though, until MRI technology (Table 1) has improved, the most impactful tool in an orthopaedic surgeon's toolbox is a thorough physical exam that delineates musculoskeletal pain generators. Identifying and communicating where an infection may exist allows MRI scans to be conducted on the 'region of interest' (Table 1) as opposed to protocols requiring scanning of an entire limb, which can take hours and necessitate sedation. In our experience, a simple Sharpie marked 'X' of the region of interest can make fast-sequence, non-sedated MRI more practical in an ER workup of a child with suspected MSKI.

What if No MRI Or the Power Goes Out?

For various reasons, MRI may not be available. In these scenarios, identifying the location of a MSKI relies even more heavily on a thorough physical exam and alternative (though inferior) imaging such as ultrasound. Importantly, one must be cognizant of "anatomical ascertainment bias" and remember that tissues other than the intra-articular space may be involved. Subsequently, judicious aspiration of all suspected tissue (see Task 2) should be conducted either in the ER or OR with the intent of assaying muscle, bone, and intra-articular fluid from the maximum point of tenderness in the child.

Infection Acts Like a Rapidly Growing Cancer
The two most common bacteria that infect children, S. pyogenes and S. aureus, produce virulence factors that
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allow them to rapidly disseminate across tissue planes and/or into the blood stream. While cases of isolated infections do occur, infections that lead to disability typically involve infection of multiple tissues of the same anatomic location (e.g., bone, muscle, and the intra-articular space), or systemic infections involving multiple body parts (e.g., bone and lung)^{5, 17, 18} (Figure 1). When disseminated disease is suspected (See Task 3: How severe is it?), the investigative team must be sure to avoid 'satisfaction of search' by not expanding their search for additional infected sites beyond the most painful joint.

Task 2: Is it an Infection, and if so, What is the Pathogen?

Rapid diagnosis of an infection and identification of the causative organism is essential to properly treat pediatric patients with suspected MSKI. First, identification of non-infectious mimicries of MSKI in pediatric patients, such as inflammatory conditions or cancer, is essential to both prevent unneeded treatment and direct critical therapy. Secondly, in cases of presumed MSKI, rapid identification of the causative organisms allows for earlier narrowing of antibiotic therapy, thus decreasing the overuse of broad-spectrum antibiotics. However, methodology and the tools available for rapid identification of infectious organisms still require improvement. Prior studies have reported culture positivity rates for patients with confirmed MSKI ranging between ~40-80%. 19-21 In the recent multicenter CORTICES study, it was found that only 1 in 3 pediatric

MSKI-related consultations produced a culture-positive identification at the time of orthopaedic consultation.¹ Negative culture results may occur because the child does not have an infection, the causative organism is difficult to culture, the incorrect tissue was sampled, or if the infection is disseminated without abscess. Additionally, the methodology of identifying organisms still primarily relies on bacterial culture, which can take days, or weeks in cases such as K. k*ingae*, to produce results. Clearly, this is an area of pediatric MSKI care that requires improvement.

Sample Early and Sample Often

Blood cultures should be taken as soon as an IV is placed in the child if not earlier. Tissue cultures can be obtained either in the ER or OR with significantly improved success after a thorough physical exam in combination with a fast-sequence MRI (Task 1). In addition to increasing the culture positivity rates of the sampled tissue, the MRI may prevent inoculating sterile tissue by inadvertently passing through infected tissue (such as muscle) on the way to the bone or intra-articular space. Importantly, a recent survey of the CORTICES group revealed significant heterogeneity across sites in regard to who collects the tissue aspirate, where the aspirate is collected, and how tissue is aspirated (data not published). For these reasons, it is essential to determine the most efficient mechanism of tissue sampling at each individual center until the method with the greatest yield is revealed. Reiterating the point above, the most important role for the pediatric orthopaedic surgeon in tissue sampling is to assure that i) the proper tissue is sampled, and ii) sufficient sample is collected in a timely manner to optimize care of the child.

Don't Hold the Antibiotics ...

If You Are Headed to the OR 'Soon'

It has long been suggested that antibiotics be held until a culture was obtained. Recent reports have demonstrated that prior antibiotic administration had no effect on culture sensitivity in patients with either local or disseminated MSKI. Furthermore, in patients with local infections, earlier antibiotic administration was found to

be correlated with shorter length of stay. ²⁰ Prior antibiotic administration did not impact positive identification of the pathogen in bone biopsy cultures, though the overall culture yields were found to be lower and inversely correlated with the duration of antibiotic therapy. ²² The current recommendation is to refrain from delaying antibiotics, particularly in patients experiencing an exuberant APR (See Task 3) given i) the limited impact on tissue culture success and ii) the clear benefit of antibiotic administration in reducing the risk for complications. ²³ The caveat to this recommendation is that it is unknown how long antibiotics can be administered before having a negative effect on cultures. In most of the previously mentioned studies the time from antibiotic administration to culture was less than 24 hours.

The Usual Suspects

Pyogenic organisms are the most common causative pathogens of pediatric MSKI with Staphylococcus aureus being responsible for 40% to 90% of cases.^{3, 24} However, epidemiological patterns of pediatric MSKI are regularly changing, attributable to dynamic mutations in the bacterial genome, use of antibiotics, and vaccinations. For example, with the advent of routine infant vaccination against *Haemophilus influenza*, the incidence of musculoskeletal infection caused by H. influenza has decreased substantially.²⁵ In another example, a 2008 study found that zero children were treated for a Methicillin-resistant *Staphylococcus aureus* (MRSA) infection in 1982; yet from 2002 to 2004, MRSA was isolated as the causative organism in 30% of children.²⁶ In a recent multicenter study of pediatric tertiary care centers conducted by the CORTICES group, it was found that Staphylococcus aureus accounted for ~65% of all culture-positive infections at the time of consultation by orthopaedic providers, of which 37.4% of confirmed staphylococcal infections were methicillin resistant (i.e., MRSA). Together, these studies illustrate that the epidemiology of MSKIs is ever-changing and up-to-date data on the common pathogens and their genetic variations must be considered when diagnosing and directing treatments.

On the Horizon: Genetic Identification of Pathogens

While traditional blood and tissue cultures support the identification of many common pathogens, standard techniques (which are almost a century old) can take days or weeks to propagate a result. For these reasons, innovative tools for identifying pathogens faster and with greater efficacy have been examined, many of which are based upon genetic amplification of bacterial DNA. For example, one such pathogen, Kingella kingae, has been rising in incidence as a causative pathogen for septic arthritis in children younger than 2 years old, in part due to improved detection methods.²⁷⁻²⁹ Unlike the more virulant staphylococcus species, K. kingae is a less virulent gram-negative bacillus that is difficult to culture under standard conditions, and even if successfully cultured, results are not available often for 2 weeks. In cases where K. kingae is suspected, PCR-based testing is now commonly utilized to detect the pathogen DNA within tissue samples. While currently outsourced by many hospitals, PCR-based testing for identification of pathogens is increasing in prevalence to meet the diagnostics needs for children with MSKI.

Given the clear utility of standard PCR for rapid identification of fastidious pathogens, Wood et al. recently examined the utility of target-enriched multiplex PCR (TEM-PCR) for identification of pathogens in pediatric patients with suspected MSKI. TEM-PCR, which was first described in 2006,³⁰ is a highly flexible, dynamic, platform capable of identifying a large spectrum of pathogens in a single sample with high sensitivity and specificity.³¹ When compared with standard culturing techniques, TEM-PCR was found to be concordant in 100% of cases and able to detect pathogens in three cases deemed negative by standard culture (two of which were K. kingae). Likewise, TEM-PCR reliably detected methicillin and clindamycin resistance in S. aureus isolates. Therefore, in addition to outperforming traditional culture techniques, these results suggest that TEM-PCR may serve as a rapid diagnostic tool for identifying the causative pathogens and resistance markers in children with MSKI.

While not yet commonly utilized in the evaluation of pediatric MSKIs, next-generation sequencing (NGS) and other high-throughput, "omics"-based techniques have been examined as ultra-sensitive means of diagnosing infections. These tools have the potential to identify a bacterium and its susceptibilities within hours as opposed to days required for traditional culturing. For example, NGS has been examined in cases of adult total joint infections as a means to identify the causative pathogen.³²⁻³⁵ NGS is optimal in this patient population given the reduced sample size required, excellent sensitivity for detecting both mono- and poly-microbial infection, and ability to be conducted on patients who were already started on antibiotics. Transcriptomics, proteomics, and metabolomics-based approaches have also been examined as diagnostic and prognostic indicators for patients with infection.³⁶ Proteomics-based assays are now in clinical use in the European Union to aid in distinguishing bacterial from viral infections. 36-38 Furthermore, proteomics-based approaches have been shown to be sensitive in prognosticating outcomes secondary to sepsis in pediatric patients.³⁹ Metabolomics has also been examined in septic patients, demonstrating that metabolites vary between healthy patients, those with sepsis who survive, and those with sepsis who do not survive. 40-44 Powerful NGS and omics-based analysis generates a large quantity of data, requires specialized analysis, and can still be costly for many institutions to perform. Given these factors, the broad application of these techniques for diagnosing pediatric MSKIs remains inapplicable at this time but holds promise for the future.

Task 3. How Severe Is the Musculoskeletal Infection?

The Acute Phase Response —
The Body's Hormonal Response to Injury
In proportion to the amount of injury, the acute phase response (APR) is activated to achieve two goals: 1) ensure survival and 2) promote tissue repair. These objectives are tackled in a temporal order. During the "survival" phase, damage control is initiated by a coordinated effort between coagulation and the survival

Conventional Wisdom:	"WBC and ESR are the main measures of the infection Task 3 provoked acute phase response and are only helpful in determining the probability of an infection."		
Old Tools:	WBC and ESR		
Shortcoming of Old Tools:	 Lack of specificity for infection Don't correlate well with disease severity and complications 		
New Wisdom:	 'Plasma acute phase reactants' (CRP, IL-6, procalcitonin) and 'Cellular acute phase reactants' (Neutrophil, Lymphocyte, Platelet, and cellular ratios) provide better sensitivity and specificity for infection Lab measures correlate with complications (especially thrombotic) Useful to measure the 'delta' to determine worsening or improving disease 		
New Tools:	Serial measurement of plasma and cellular markers of the APR		

inflammatory response to temporarily seal off compartments with a fibrin/platelet seal. In addition to stopping bleeding, this sealant promotes ingress of survival inflammatory cells which help reduce the susceptibility to infection. For example, neutrophils, in cooperation with the host's coagulation response, work to trap bacteria in DNA neutrophil extracellular traps (NETs) and fibrin webs and release chemotoxins to kill pathogens. Meanwhile, macrophages clear the trapped bacteria. Once survival is ensured, the APR transitions to a reparative inflammatory response that paves the way for revascularization and regeneration of the damaged tissues. In an acute injury, this series of events occurs over several weeks, allowing for a timely recovery^{45, 46} (Figure 2).

Morbidity and Mortality is Relative to a Prolonged or Exuberant APR
Unlike an acute injury, in the context of a MSKI, tissue damage is continual as the infection worsens or spreads. As a result, the regulated and coordinated nature of the APR can be lost. 9,45 After invading the body, bacterial proliferation and the expression of virulence factors allow pathogens to evade the host containment mechanisms (fibrin/DNA webs) and migrate through tissue planes causing damage to neighboring tissue.

Thus, as opposed to single isolated infections, the APR in combinatory infections is more exuberant, correlating with the amount of tissue infected and the duration of the infection. Furthermore, in addition to the "volume" of an infection, the bacteria's capacity to hijack many of the acute phase reactants can further drive an exuberant "survival" APR (Figure 3A).

When dysregulated, an exuberant survival APR drives inflammation and coagulation to pathologic levels leading to thrombotic complications, such as septic pulmonary emboli, deep vein thrombosis, and potentially death. Given the essential role for vascularity in developing bone, thrombosis following an exuberant APR can also lead to avascular necrosis of the epiphysis, metaphysis, or diaphysis, potentially leading to loss of joint function and abnormal limb development. For these reasons, rapid diagnosis and treatment of an infection is essential to mitigate an exuberant or prolonged APR, thus reducing the risk of complications, patient morbidity, and mortality (Figure 3B).

Measuring the APR to Assess MSKI Severity Accurately determining the severity of a MSKI is essential to managing patient morbidity and mortality. Previously, laboratory values were primarily utilized at

admission to assist with diagnosis of MSKI with little use after the initial diagnosis. Over the past ~10 years, studies have demonstrated the clinical utility of measuring the APR not only at the time of admission to aid in diagnosis, but also serially throughout a case to measure the severity of the disease, monitor the patient's response to treatment, and prognosticate the risk for complications. While a patient's presenting symptoms, such as fever, indicate the activation of the APR, more sensitive measures of plasma reactants and cellular effectors are required to discern the severity of the APR and accurately prognosticate the risk for complication. Importantly, while there are over 1,000 acute phase reactants, not all markers are created equal. Instead, they vary in both sensitivity and specificity relative to the type of injury. For these reasons, pediatric orthopaedic physicians must be aware of the advantages and limitations of each marker evaluated during diagnostic workup and assessment of patient prognosis.

Key Plasma Acute Phase Reactants
Within plasma, the "survival" APR can be sensitively
quantified in real-time through serial measures of

inflammation and coagulation. C-Reactive protein (CRP) is a well-validated, dynamic, acute phase reactant that elevates in response to inflammation. ²²⁻²⁵ In current clinical practice, CRP is utilized as both a diagnostic and prognostic tool at the time of consultation for MSKI. In prior retrospective and prospective studies, CRP has been shown to be effective for early diagnosis of an infection within 4-6 hours of symptom onset. Furthermore, given that CRP levels rapidly elevate in proportion to the amount of tissue inflammation, admission CRP levels have been demonstrated to sensitively predict the severity of a MSKI.⁵

Given the dynamic and sensitive nature of CRP, studies have examined the utility of serial measures to better monitor disease progression and response to treatment. 47-49 For example, assessing peak CRP levels has been demonstrated to be a strong predictor of vascular complications in patients with MSKI, such as venous thromboembolism. Specifically, it was found that for every 20 mg/L increase in peak CRP, the risk of thrombosis increased 29%. 17 Beyond prognosticating the risk for complication, serial measures of CRP can be

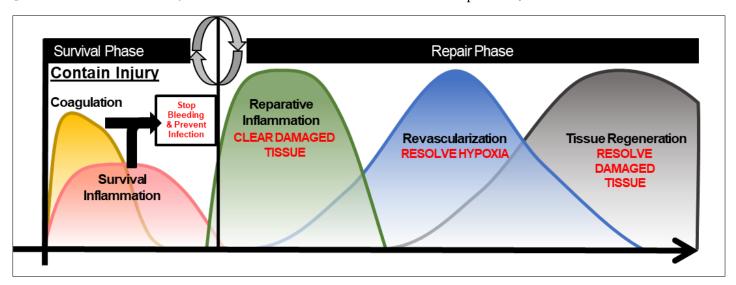


Figure 2. The Acute Phase Response – The Body's Response to Injury. A) Following an injury, in order to ensure survival, the body must first contain the injury by resolving bleeding and preventing infection. This is accomplished through the coordinated activation of the coagulation cascade (i.e., hemostasis) and the survival inflammatory response. Once bleeding has been stopped and any infectious pathogens are contained, the body can transition to the "reparative phase" where inflammatory components, such as macrophages, can enter the tissue and begin to clear dead cellular debris, bacteria, and damaged tissue. Once cleared, revascularization and tissue regeneration of the damaged tissues can occur to reestablish the pre-injury physiologic state. (Figure permission: Schoenecker Laboratory)

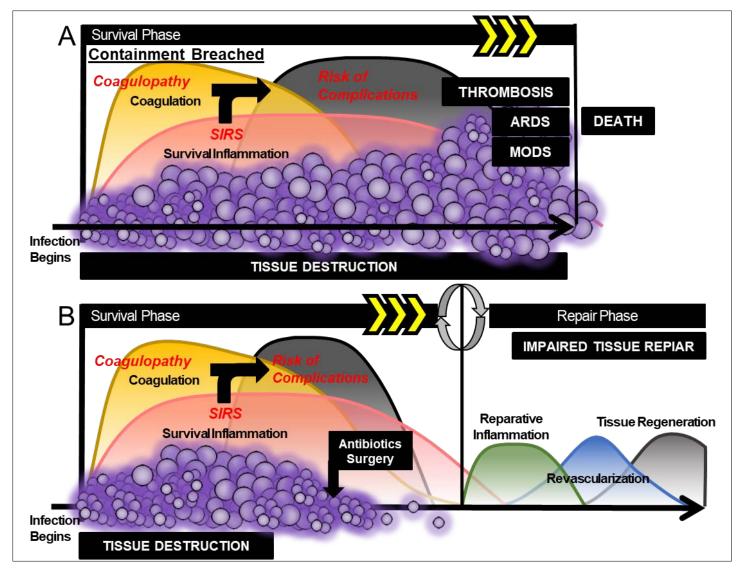


Figure 3. The Acute Phase Response During Infection. A) As infection progresses, the survival phase of the APR will progressively increase in magnitude as it attempts to respond to the growing infection and tissue destruction. The duration and severity of activation of coagulation and survival inflammation proportionally increases the patient's risk for complications such as thrombosis (leading to AVN), acute respiratory distress syndrome (ARDS), multiorgan dysfunction (MODS), and even death. B) Through intervention with surgical debridement and antibiotic administration, the pathogen onslaught can be reduced, allowing the survival phase of the APR to be sufficient to stop bleeding and trap the remaining bacteria. However, as a result of the exuberant survival APR activated in response to infection, patients may still experience impaired tissue healing following the resolution of the infection (B-Repair phase). (Figure permission: Schoenecker Laboratory)

utilized to assess response to treatment. In MSKIs, if a treatment is effective, the CRP and other acute phase reactants should begin to return to normal levels.⁴⁵ If values do not return to baseline or continue to increase within ~48 hours of intervention, this can indicate to the medical team that the prior treatment was insufficient and further intervention is likely necessary (Figure 4).

Another classically measured plasma APR value is erythrocyte sedimentation rate (ESR). In the context of injury or infection, ESR has been examined as a surrogate measure for fibrinogen and the ongoing containment of the injury to prevent bleeding and reduce susceptibility to infection (Figure 2 & 3-Survival APR). Compared to CRP, ESR is a less sensitive marker for the

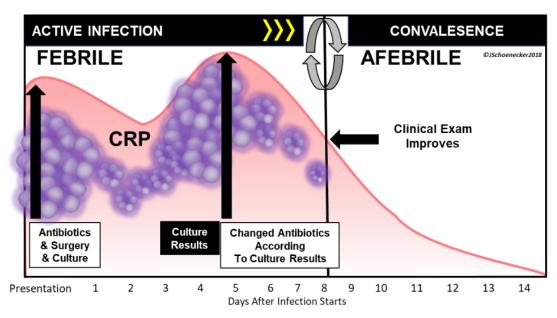


Figure 4. Utility of Serial Laboratory Values of the APR within a Case. Trends, or the 'Delta' in CRP can be useful in assessing disease progression and treatment efficacy in pediatric patients with MSKI. Early treatment is essential in treating MSKI, with antibiotics and surgery leading to a decrease in CRP over the first 2 days. However, when CRP begins increasing again over day 3 and 4, this can indicate to the treating physician that further intervention may be necessary. At this time, culture results showed inadequate antibiotic therapy and antibiotics were adjusted. After this point, the CRP once again began trending downward and the clinical exam improved. The body then entered the convalescent stage where tissue repair can begin. This case highlights the importance of both culture-directed therapy and the capacity for serial APR measures to assist with patient care. (Figure permission: Schoenecker Laboratory)

APR and can also produce misleading data for assessing infections, given that confounding conditions, such as pregnancy, obesity, and anemia, which all result in an elevated ESR.^{50, 51} Furthermore, reflective of fibrinogen's role in containment, ESR is a longer acting and less dynamic acute phase reactant. Therefore, while ESR may not perform well at admission for predicting the presence of an infection, monitoring ESR may be useful to assess long-term recovery of patients as they enter the repair phase of the APR.⁵²

Up and Coming Plasma Acute Phase Reactants
Although more expensive than CRP, plasma
concentration of procalcitonin has been proposed as an
alternative indicator of the APR in cases of infection.^{53, 54}
Like CRP, procalcitonin is rapidly produced by the liver
in response to inflammation. As such, serum
concentrations are normally undetectable but can
increase a thousandfold in the setting of systemic
bacterial infections.⁵⁵ In the setting of sepsis,

procalcitonin has also been shown to be useful in measuring treatment response with a decline in its levels expected within 72-96 hours of treatment initiation.⁵⁶ One meta-analysis of adults with bone and joint infects reports that a procalcitonin of less than 0.3 ng/mL suggests a low suspicion for infection, while a procalcitonin of greater than 0.5 ng/mL raises concern for infection.⁵⁷ To date there are few studies that examine the use of procalcitonin in the context of pediatric musculoskeletal infection. Given the above scientific premise and multiple studies suggesting advantages of procalcitonin over CRP,⁵⁸⁻⁶³ future retrospective and prospective studies of procalcitonin in pediatric MSKI are warranted.

Interleukin-6 (IL-6) is the principal initiating factor of the APR. IL-6 is stored in musculoskeletal tissue and released immediately following injury or infection where it then travels to the liver to promote the expression of acute phase reactants, including CRP. Therefore, IL-6

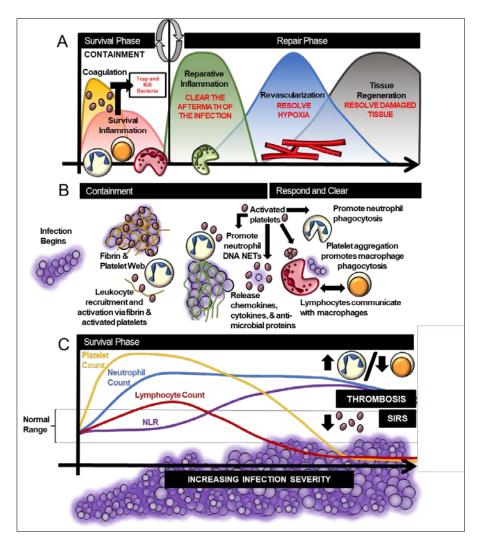


Figure 5. The Cellular APR Following Infection—Always get a Differential A) Following the establishment of an infection and the associated tissue destruction, much like an acute injury (Figure 2), the body must first stop bleeding and contain the infection. This is accomplished through the coordinated activities of the coagulation and survival inflammatory systems during the "survival" phase of the APR. B) Coagulation components, specifically fibrin and platelets, aid in containing the bacteria to the site of infection in addition to serving as a platform for recruitment of leukocytes. Once bound to fibrin, activated platelets can directly aggregate and signal to leukocytes. Through these interactions, an important second containment mechanism is activated—the production of NETs. As the infection is contained, pro-inflammatory macrophages and neutrophils begin to phagocytose invading pathogens. Through engulfing the pathogens, macrophages can then communicate with lymphocytes as part of the innate immune response. Together, these coordinated activities of the coagulation and survival inflammatory systems are essential to control, contain, and combat an infection. C) As the infection progresses and increases in severity, the cellular components of the APR can become dysregulated. Platelets, which initially increase in number to assist with fighting an infection, can begin to diminish when the infection is exuberant and prolonged, reflecting their consumption, sequestration, or clearance from circulation. Likewise, neutrophils and lymphocytes both elevate in response to infection. As the infection increases in severity and/or prolongs, lymphocytopenia can occur, resulting in a greater NLR. Thus, measures of decreasing platelet count and increasing NLR together have been found in cases of adult infection to associate with poor outcomes such as thrombosis and systemic inflammatory response syndrome (SIRS). While less examined to date, there is ample scientific premise for the use of both platelet count and NLR as a means to assess severity and outcome in patients with pediatric MSKI. (Figure permission: Schoenecker Laboratory)

Table 2. Snapshot – Platelet-Leukocyte Aggregates in Infection				
Platelet-Neutrophil Aggregates	Platelet-Monocyte/Macrophage Interactions	Platelet-Lymphocyte Aggregates		
 Platelets promote neutrophil extravasation at the site of infection⁸⁷ Platelets stimulate the release of DNA NETs (i.e., NETosis), which serve as webs for efficient capture and destruction of circulating bacteria^{84, 88, 89} Activated platelets promote neutrophil phagocytosis^{90, 91} Activated platelets promote the release of reactive oxidative species^{92, 93} Platelet interactions drive Mac-1 expression on neutrophils to recruit additional leukocytes, such as monocytes, to the site of infection. 	 Monocyte-platelet aggregates have been detected in forms of infection Platelets promote monocyte extravasation at the site of infection⁸⁷ Activated platelets preferentially interact with inflammatory CD16+ monocytes and promote a proinflammatory phenotype^{94, 95} During tissue repair, platelets can also reduce inflammatory response by downregulating IL-6 and TNF-alpha released from the monocyte CXCL4 released into microenvironments by activated platelets supports the differentiation of monocytes into macrophages⁹⁶ and specialized antigen presenting cells⁹⁷ Platelet interactions with monocytes can modulate cytokine release⁸⁷ Platelets aggregate around bacteria captured by liver-resident macrophages to aid in their clearance⁹⁸ 	 Platelet-lymphocyte aggregates are elevated in certain types of infection Platelet-lymphocyte interaction can enhance or diminish leukocyte cytokine production⁸⁷ Platelet interaction can greatly enhance lymphocyte adhesion⁹⁹ Platelet-lymphocyte aggregates are thought to modulated T-cell recruitment to support the innate immune response¹⁰⁰ 		

provides the earliest measurable response to tissue damage, ⁶⁴ even though few studies examining the diagnostic capacity of IL-6 in the context of MSKI have been conducted. This is in part due to the limited availability for testing IL-6 in the clinical setting, its short half-life in plasma, and the absence of clinical standardization. For these reasons, measurement of IL-6 remains primarily within the research setting.

Taken together, these studies demonstrate the clear prognostic and diagnostic utility for serially assessing plasma measures of the "survival" APR in cases of suspected pediatric MSKI. These easily attainable measures can be incredibly useful for treating physicians to not only diagnose and assess the severity of the infection, but also to determine the effectiveness of treatment.

Key Cellular Effectors as Indicators of the APR – Always Get a Differential In addition to plasma acute phase reactants, changes in cellular effectors can also be sensitive indicators of the "survival' APR (Figure 5A). Broadly, white blood cell (WBC) counts are commonly utilized to assess the presence of an infection. However, WBC counts are one of the least sensitive measures for the diagnosis of a pediatric MSKI. In addition to being variable with age, prior studies have demonstrated a wide range in the incidence of elevated WBC counts (25%-73%) amongst osteomyelitis patients. Furthermore, similar WBC values have been reported in pediatric patients with inflammatory (non-infectious) etiologies, local infections, and disseminated infection. This demonstrates that elevated WBC counts alone are not sufficient to confirm the presence or assess the severity of a MSKI.⁶⁵

Alternatively, analysis of specific subtypes of leukocytes, such neutrophils, lymphocytes, and their relative proportions, has been found to be more sensitive for assessing the presence or severity of an infection. As opposed to measuring the WBC without a differential, which is "like trying to decide who won an election by

	Inflammatory (Non-Infectious)	Local Infections	Disseminated Infections	Disseminated Infection + Complication
8	All of the following (if available) must be TRUE: Negative blood culture Negative local culture The criteria for "local" or "disseminated infections" are not met	One of the following must be TRUE: Imaging diagnostic for osteomyelitis or pyomyositis in one anatomical site Local culture positive AND/OR fluid/tissue consistent with infection (grossly purulent, cell count >50,000, and/or positive PCR) One positive blood culture The criteria for "disseminated infections" are not met	For two or more anatomic sites, at least one of the following must be TRUE: Imaging diagnostic for osteomyelitis or pyomyositis Local culture positive AND/OR fluid/tissue consistent with infection (grossly purulent, cell count >50,000, and/or positive PCR) Two or more positive blood culture	In addition to meeting the criterial for "disseminated infections," at least one of the following must be TRUE: • Thromboembolic disease such as: • Deep vein thrombosis • Pulmonary embolism • Avascular necrosis • Multiorgan Failure • Pleural Effusion • Pathologic Fracture • Limb/Joint Deformity • Amputation • Sequestration/Involucrum • Death
Example	Transient synovitis	Isolated distal femoral osteomyelitis with no subperiosteal abscess Isolated septic hip	Distal fibular osteomyelitis with subperiosteal abscess Septic hip with surrounding pyomyositis	Patient with proximal femur osteomyelitis with subperioster abscess and adjacent pyomyositis that experiences multiple venous thromboembolisms

just counting how many people voted¹," understanding a differential provides invaluable information regarding the infection and can tell you "who is winning the election." Neutrophils are an essential cellular player in innate immunity that activate in response to the APR and bacterial invasion. In addition to directly binding and phagocytosing pathogens, neutrophils also aid in trapping and killing bacteria in the extracellular space by producing neutrophil extracellular traps (NETs), reactive oxygen species, and other cytotoxic molecules^{66, 67} (Figure 5B). Given these essential roles, neutrophils are the most abundant leukocyte in circulation and their levels are tightly regulated.⁶⁸ As such, elevation in neutrophil number has long been utilized as a prognostic indicator of infection. However, when evaluating the severity of infection, neutrophil count alone does not perform well.⁶⁹ For these reasons, many studies have

begun to examine cellular ratios, such as the neutrophil to lymphocyte ratio (NLR), as a more sensitive predictors of disease severity and prognosticators of patient outcomes.

While not yet commonly utilized in pediatric MSKI, NLR has been demonstrated in numerous studies to sensitively detect infections and prognosticate disease severity and patient outcomes (Figure 5C). For example, in patients hospitalized for fever with an unknown origin, NLR was found to be higher in patients with a bacterial infection than in those with a viral infection.⁷⁰ Furthermore, NLR was able to outperform CRP and WBC as an early indicator for septicemia.⁷¹⁻⁷³ In patients with community-acquired pneumonia, admission NLR

¹Dr. Isaac Thomsen – Vanderbilt University Pediatric Infectious Disease

within the emergency department was able to predict disease severity and outcomes with a higher prognostic accuracy than CRP, WBC, or either cellular measure alone.⁷⁴ Finally, when considering patient outcomes, elevated NLR was an independent marker for mortality in patients with bacteremia⁷⁵ and a strong positive predictor for treatment failure and 90-day mortality in adult patients with septic arthritis.⁷⁶

Small but Mighty – Role of the Platelet in Assessing MSKI Presence and Severity Platelets are the first line of defense against pathogen invasion at a site of injury. Consistent with this role, platelets are capable of directly interacting with bacteria, 77, 78 engulfing bacteria, 79 and releasing bactericidal molecules from their granules. Furthermore, from a hemostatic perspective, platelets assist with pathogen containment by supporting fibrin formation at the site of injury, serving as a barrier, and reducing the spread to surrounding tissues (Figure 5B). As a result of ongoing research, platelets are now increasingly recognized as thrombo-inflammatory cells that respond to both hemostatic/thrombotic and immunomodulatory signals in circulation. Activated platelets interface with the innate immune response by releasing a myriad of chemokines and cytokines from their α-granules, which can alter the function of surrounding tissues, priming leukocytes and endothelium for adhesion and extravasation.80,81

In addition to their individual impact on fighting MSKI, platelet activation through thrombin receptors^{82, 83} or toll-like receptors⁸⁴ also stimulates the formation of platelet-leukocyte aggregates.⁸⁵ The direct interaction of platelets and leukocytes (neutrophils, monocytes, and lymphocytes) aids in the honing and recruitment of leukocytes to sites of injury or infection by supporting leukocyte rolling and attachment to adherent, activated platelets. Furthermore, coupling with a platelet transforms the leukocyte phenotypes, supporting more cytotoxic and inflammatory activities (Table 2 & Figure 5B). Thus, platelets play an essential role in supporting the containment and removal of

pathogens by the innate immune response that is critical to survival. 86, 87

In addition to their ease for clinical assessment, elevated platelet counts have long been examined as a prognostic indicator for infection. In pediatric MSKI, elevated platelets effectively discriminate between pediatric patients with or without osteomyelitis. 101 However, platelet count, unlike most other APR measures, is dichotomous, such that both abnormally high as well as abnormally low platelet counts are associated with adverse outcomes. For example, in adult patients undergoing a total knee arthroplasty, while abnormally high platelet levels prior to surgery were associated with a higher rate of minor adverse events (such as wound dehiscence or blood transfusion), abnormally low platelet values were associated with a higher rate of major adverse outcomes (such as sepsis/septic shock, stroke, cardiac arrest, thromboembolism, or a pulmonary embolism). 102 Given their essential role in supporting an immune response, high platelet counts can contribute to excessive inflammation as part of an exuberant APR. However, as a result of an exuberant APR, platelet counts in circulation can diminish, reflecting their consumption (fibrin/platelet complex), sequestration (cellular bound/tissue depot), or clearance (splenic macrophages)¹⁰³ (Figure 5C). Consistently, thrombocytopenia has been associated with mortality in septic patients. This clear dichotomy illustrates that, depending on when platelets levels are assessed, both abnormally high as well as abnormally low platelet counts can be associated with adverse outcomes. 67, 103, 104

Clinical Application of Cellular Markers of the APR Together these studies illustrate the diagnostic and prognostic capacity for cellular measures of the APR in patients with suspected infections. While less examined to date, there is ample scientific premise for the use of both platelet count and NLR as a means to assess severity and outcome in patients with pediatric MSKI. Given the ease and cost effectiveness of such measures, future retrospective and prospective studies are warranted. Likewise, as research progresses, future novel

diagnostic markers, such as platelet-leukocyte aggregates, may further improve the sensitivity and timeliness of detecting infections; however, currently, such assessments are not routinely available in clinical laboratories. ¹⁰⁵

Classification System for MSKI Severity in Pediatric Patients

Presently, many studies assessing pediatric MSKI divide patient populations relative to their diagnosis, such as osteomyelitis, pyomyositis, septic arthritis, etc. ¹⁰⁶ An inherent limitation to this practice is that clinical presentation, treatment, and patient prognosis are highly variable within each diagnostic cohort. ¹⁰⁷ Furthermore, as discussed above, MSKI is often not isolated to a single tissue, thereby further complicating the stratification of patients based on diagnosis alone. For these reasons, classification systems based on MSKI severity and degree of dissemination have been developed. ^{5,6}

A study by Mignemi (Johnson) et al. utilized the following operational definitions to stratify patients with suspected MSKI into three categories: inflammation (non-infectious), local infection, and disseminated infection⁵ (Table 3). Utilizing these criteria, the authors found that more severe, disseminated disease positively correlated with both prolonged hospital stays and markers of the APR. Across these three categories, a recent study by Benvenuti et al. used mathematical modeling to demonstrate that CRP, pulse rate, and temperature together can accurately predict MSKI severity classification at presentation. Specifically, this model found that the odds of a more severe outcome increased by 30% for every 10 U increase in CRP.6 Improving upon this classification system, it was noted that pediatric patients with disseminated disease who did or did not experience complications had varying APR profiles;¹⁷ thus, a fourth category (disseminated infection + complication) has been established (Table 3). Since this classification system does not rely on anatomic diagnosis or identification of tissue involvement, early identification of disease severity, and therefore patient prognosis, is possible. Future prospective studies are Copyright @ 2020 JPOSNA

warranted to validate the clinical utility of this classification system and model.

Virulence Factors Drive Disease Severity Through Attacking the Cellular APR As highlighted above, pyogenic organisms are the most common causative pathogens of pediatric musculoskeletal infection with S. aureus being responsible for 40% to 90% of cases.^{3, 24} In addition to antibacterial resistance genes, S. aureus has acquired virulence factors to help the pathogen evade the host's cellular APR, 108, 109 and as a result have been associated with elevated inflammatory responses in pediatric MSKI.¹¹⁰ Though the incidence varies between patient populations, 111-120 two examples of virulence factors observed in community-associated MSSA and MRSA are Pantone Valentine Leukocidin (PVL) and Leukocidin AB (LukAB). Expression of either PVL or LukAB promotes host leukocyte destruction through toxin-mediated pore formation and cellular lysis. 121-124 By evading the host's cellular APR, PVL and LukAB can drive S. aureus infection severity by promoting dissemination, tissue necrosis, and elevating the inflammatory response. 121, 123, 125-127 Thus, treating physicians should consider the presence of acquired virulence factors, particularly in cases of communityassociated S. aureus infections (both MSSA and MRSA), to better prognosticate MSKI disease severity and patient outcomes.

Task 4. How to Treat the Musculoskeletal Infection

Hit the Bug with Bug Juice and Drain the Purulent Fluid
Antibiotics and surgical debridement are paramount for cessation of the continuous injury caused by a MSKI^{9, 45} (Figure 3B). As noted above, regulation of the APR is critical, as continuous exuberant activation can lead to devastating complications accounting for the majority of morbidity and mortality in pediatric patients with MSKI. 45 In this final section, we will highlight common treatment modalities, focusing on those aimed at combatting the MSKI and also therapeutic options being examined to combat an exuberant host APR.

Conventional Wisdom:	"MSKI requires a PICC." "MRSA is way worse than MSSA." "The sun never sets on a septic hip." "SIRS and SIC are untreatable."	
Old Tools:	 PICC lines Other than antibiotics, treating MRSA differently than MSSA X-ray and ultrasound Ignoring SIRS and SIC 	
Shortcoming of Old Tools:	 PICC associated complications Anatomical ascertainment bias – focus on intra-articular processes Assumption that MSSA causes less severity than MRSA 	
New Wisdom:	 Oral antibiotics are as efficacious as intravenous for long-term treatment MSSA, or community acquired S. Aureus, is gaining MRSA virulence fact that make it as equally toxic to the patient Bone, muscle, and/or the intra-articular space may be infected 	
New Tools:	 Oral antibiotics Precision debridements Pharmacologics to treat the exuberant Acute Phase Response (SIRS and SIC) 	

Common Antibiotics Used in Pediatric Orthopaedics

Prior to the advent of antibiotics, the mortality rate of acute hematogenous osteomyelitis in children was as high as 40%.^{2, 3} Fortunately, in current day medicine, the mortality rate from pediatric infections has dropped tremendously in recent years.^{5, 26, 128} Antibiotics continue to be the first line of therapy for MSKI. In addition to culture results, patient factors can also inform antibiotic selection. As discussed above, rapid identification of the causative organisms is important given that it allows for earlier narrowing of antibiotic therapy, thereby decreasing the overuse of broadspectrum antibiotics. Thus, in addition to collaborating with colleagues who specialize in infectious disease, it is important for pediatric orthopaedic surgeons to have a broad understanding of the advantages and disadvantages of common antibiotics used to treat Copyright @ 2020 JPOSNA

MSKI. These include beta-lactams, glycopeptides, lincosamides, lipopeptides, rifampin, and to a lesser degree, aminoglycosides (Table 4).

Intravenous vs. Oral Administration:
Is a PICC Line a Thing of the Past?
Traditionally, the duration and route of antibiotics administered is dependent on the institutional experience, the patient's response, and the type of tissue affected. For example, 2-4 weeks of intravenous (IV) antibiotics is often recommended for osteomyelitis followed by oral antibiotics for a total of 6-8 weeks.
Some institutions have promoted shorter durations of IV antibiotics until CRP has decreased by 50% followed by 2-4 weeks of oral antibiotics. 129 In either case, IV antibiotics are commonly administered through a peripherally inserted central catheter (PICC). Beyond providing a secure route for vascular delivery

Table 4. Snapshot – Antibiotics for Treating MSKI Every Orthopaedic Surgeon Should Know					
Class	Beta-Lactams	Glycopeptides	Lincosamides & Aminoglycosides	Rifampin	Lipopeptides
MOA & Key Clinical Features	 Rapid bactericidal activity by lysing cell wall Overall, well-tolerated with few side effects Allergy is commonly reported; many patients have outgrown these allergies Bacterial resistance is common Administered IV and PO 	Bacteriostatic effects by inhibiting bacterial cell wall formation Limited bacterial resistance Administered IV or topically	Elicit bacteriostatic effects by binding to bacterial ribosomal subunits → inhibiting protein synthesis Lincosamides inhibit 50s subunit Aminoglycosides inhibit the 30s subunit	 Elicit bactericidal effect by inhibiting bacterial RNA polymerase during replication Administered IV or PO Potential hepatotoxic effects if administered at high concentrations 	Rapid, concentration- dependent bactericidal activity Distinct mechanism of action by disrupting multiple aspects of the bacterial cell membrane Limited bacterial resistance Administered IV
Therapeutic Options	Anti-staphylococcal penicillin: (e.g., oxacillin, nafcillin, methicillin, dicloxacillin) Resistant to beta- lactamase enzyme commonly produced by S. aureus Used for MSSA infection Cephalosporins: 1st generation: (e.g., cefazolin (ancef), cephalexin (Keflex), cefadroxil) are commonly utilize to treat gram positive MSKI 3rd generation: (e.g., cefotaxime, ceftriaxone, cefixime, and cefdinir) have increased stability against gram negative pathogens 5th generation: (e.g., ceftaroline and ceftobiprole) include activity against MRSA	as empiric therapy in cases where MRSA, enterococcal, or other serious gram-positive infections are suspected Once culture results are available, narrowing to alternative agents is essential Vancomycin is inferior to beta- lactams in susceptible strains New Therapeutics: (e.g., dalbavancin and oritavancin) Very long half- lives and simplified dosing regimens Potential for	Clindamycin: Effective against gram positive and anaerobic pathogens effective at limiting toxin-mediated illness (e.g. Group A streptococcus and S. aureus) given their effect on protein synthesis Excellent activity against MRSA Growing bacterial resistance, up to 20% in some regions Administered PO Aminoglycosides: (e.g., gentamicin, tobramycin, amikacin) Broad spectrum activity effective against gram negative organisms Narrow therapeutic window Significant ototoxicity and nephrotoxicity	Rifampin: Effective against a wide variety of grampositive and gramnegative organisms, particularly staphylococcus Administered in combination with other agents to increase potency	Daptomycin: Effective against gram positive pathogens, including MRSA Effective alternative in cases where vancomycin is ineffective Studies presently ongoing examining optimal dosing Randomized clinical trials still required for MSKI
Highlights for MSKI	 Cephalexin is well absorbed orally and has good bone penetration 5th generation cephalosporins can be useful in patients where disseminated disease is suspected 	Useful in patients where disseminated disease is suspected	great oral	Extreme tissue penetration Useful adjunct therapy to treat MSKI where indwelling hardware or prostheses are present	 Excellent soft tissue and bone penetrance Has bactericidal activity within biofilms

of antibiotics, the use of a PICC line in pediatric patients is riddled with complications ranging from occlusion of the line to more serious complications such as infection or thrombosis. 130-132 For these reasons, physicians have begun to compare the effectiveness (i.e., treatment failure) of oral vs. IV antibiotic administration in pediatric patients with MSKI. A retrospective cohort study by Karen et al. in JAMA *Pediatric* illustrated that across 36 participating Children's Hospitals, PICC and oral antibiotic administration after discharge were equally as effective in patients with acute hematogenous osteomyelitis, yet patients with a PICC had a higher risk of returning to the emergency room or hospitalization for an adverse outcome. 133 This study highlights the need for physicians to challenge the long-standing belief that a PICC is essential for antibiotic care. As oral antibiotics continue to improve in efficacy and tissue penetration, IV administration beyond the time of hospitalization may not offer increased efficacy. Future prospective studies in cases of more severe, disseminated, infections will be essential for understanding the true potential for negating use of a PICC and their associated complications in pediatric patients with MSKI.

Antibacterial Resistance Impact on MSKI Severity As previously highlighted, physicians are now observing an increased rate of patients with MRSA associated MSKI as a result of antibiotic administration and pathogen evolution. While this trend brought great concern to the medical community, the relative severity of infections caused by MRSA vs. MSSA remains controversial. Clinically, reports have suggested that compared to non-MRSA MSKI, patients with MRSA endure a more robust APR, have a longer hospital stay, and experience a higher rate of complications such as deep vein thrombosis, septic pulmonary emboli, and pathologic fractures. 134-138 Furthermore, in adult patients hospitalized for MRSA or MSSA infections, those with MRSA were reported to have poorer outcomes, including longer hospital stays, greater rates of complications, and increased mortality. 139

Alternative to these reports, a recent retrospective study by An et al. demonstrated that in pediatric MSKI patients with Staphylococcus aureus infections, no significant difference in length of stay, days with a fever, or duration of antibiotics was observed between patients with MSSA vs. MRSA. 140 In this retrospective study, patients with MRSA required significantly more operative interventions than MSSA; however, CRP (as a measure of the APR), temperature, WBC count, pulse, and respiratory rate were all unable to differentiate patients with MRSA from those with MSSA. 140 This finding aligns with the variable success of prediction algorithms for distinguishing between MRSA vs. MSSA by assessing four predictive parameters: a temperature higher than 100.4°F, a WBC count greater than 12,000 cells/µL, a hematocrit level less than 34%, and a CRP level greater than 13 mg/L.141 While initial reports found that 92% of all patients with all four predictors suffered from MRSA, subsequent studies have found diminished success (50%) using this algorithm. 142 Together, these reports suggest variance in relative MRSA to MSSA virulence may exist both regionally and between institutions. For these reasons, validated prediction models that perform well at one institution may be ineffective at other sites given temporal and geographical variance in virulence patterns. Regardless, molecularly, MSSA is gaining the virulence factors that were once only prevalent in MRSA. Thus, although at one time it was beneficial to determine the difference between MRSA and MSSA to prognosticate on the severity of the disease, the dynamic genetic evolutions of these infectious organisms are quickly rendering this to be an arguable point.

Indications for Surgical Management – Culture, Excise, and Source Control
In collaboration with antibiotic administration, in order to obtain cultures, reduce the infectious burden and mitigate the associated APR, surgical debridement of the infected tissue is often required. Numerous factors should be considered when directing surgical intervention in these patients. For example, relative to assessing the severity of disease, any patient who is

physiologically unstable secondary to a MSKI should be considered for urgent surgical debridement. This is particularly important in cases of rapidly progressing and destructive infections, such as necrotizing fasciitis. He general genera

Pharmacologic Management of the APR
As highlighted above, overactivation of the APR in response to a severe, disseminated MSKI can result in marked changes in inflammation and coagulation.
Together, hyperinflammation (also referred to as systemic inflammatory response syndrome (SIRS)) and sepsis-induced coagulopathy (SIC) increase patient morbidity and mortality. Thus, the most effective means to prevent and treat an exuberant APR is to mitigate the infection with antibiotics and surgical debridement. To compliment these efforts, numerous studies in the adult population have begun to examine the therapeutic benefit of correcting hyperinflammation and the coagulopathies with the aim of reducing the morbidity and mortality of infection. 145-148

Combating Sepsis-Induced Coagulopathy (SIC) In the past, a clinically meaningful infection-related coagulopathy was thought only to occur when patients met the clinical criteria of disseminated intravascular coagulation (DIC). Recently, the International Society for Thrombosis and Hemostasis (ISTH) amended the diagnostic criteria for infection or trauma-induced coagulopathies recognizing that the diagnostic criteria for DIC were very specific but not sensitive for many meaningful clinical coagulopathies. Since there is not (yet) a specific term for a MSKI provoked, non-septic

induced coagulopathy, for simplicity, this condition will be placed under the new ISTH term 'sepsis induced coagulopathy' or SIC.

One of the most difficult barriers to treatment of SIC is the underlying acquired deficiency in coagulation factors. For example, consumption of anti-thrombin and protein C secondary to infection makes it so that anticoagulants, such as heparin and heparinoids, are ineffective. 143, 148 Therefore, the most logical means to treat SIC is to replace the consumed coagulation factors. This has been attempted clinically by multiple pharmacologic means. In critically ill patients, fresh frozen plasma (FFP) was examined – though results varied clinically in part due to FFP inability to completely restore depleted coagulation factors (made evident by its PT-INR of 1.6). Alternatively, in adult patients with SIC, administration of anti-thrombin and recombinant thrombomodulin (which activates protein C) without restoration of the procoagulants was found to improve survival. 150-152 Finally, bypassing the need for direct replenishment of factors, studies have alternatively focused on improving coagulation factor function as a means to treat SIC. Given that vitamin K is an essential cofactor for factors II, VII, IX, and X, protein C, and protein S, vitamin K supplementation has been examined in the setting of infection for the treatment of both hyper- and hypo-coagulability with no reported adverse event. 143, 145, 153, 154 In the authors' opinion, when considering potential morbidity associated with severe disseminated MSKI and the potential benefits (with minimal side effects) of vitamin K, administration may be worthwhile in cases of severe disease.

Paralleling the consumption of coagulation factors, severe prolonged infections can result in the consumption of platelets as discussed above. Given platelets' essential role in both coagulation and prevention of infection, improving platelet counts via transfusions have been suggest as a therapeutic means to improve patient outcome in cases of severe infection. ¹⁵⁵, ¹⁵⁶ While research in transfusion medicine has greatly improved the safety for transfusion products, ¹⁵⁷ the half-

life of a transfused platelet is short; thus, multiple transfusions are often required to improve patient levels. To date, the therapeutic benefit of replenishing either platelet or coagulation factors has not been examined in the field of pediatric MSKI. Given the strong scientific premise from studies of adult disseminated infections prone to complication, future studies in the pediatric sector are warranted.

Combating Systemic Inflammatory Response Syndrome (SIRS)

As discussed above in detail, measures of inflammation are powerful predictors of MSKI severity and risk for complications in pediatric patients. In cases of severe or disseminated MSKI, the development of SIRS can lead to reversible or irreversible organ dysfunction as well as death. To pharmacologically combat SIRS, prior studies have examined either the use of intravenous immunoglobulin (IVIG) or corticosteroids.

In adult cases of Group A Streptococcus infections, IVIG was theorized to help clear bacteria from the body and neutralize the superantigens, thereby reducing the systemic SIRS. ¹⁵⁸⁻¹⁶² Furthermore, IVIG administration in pediatric patients with hematological disorders is effective at increasing platelet count, ¹⁶³ thus illustrating a potential benefit for pediatric patients combating an exuberant APR. To date, while IVIG has been applied to a broad range of applications, no directed trial in pediatric MSKI has been conducted. Future prospective trials would be required to discern the potential benefit of IVIG in cases of severe or disseminated pediatric MSKI.

Corticosteroid use in cases of severe infection or sepsis remains controversial in terms of efficacy. While the CORTICUS (Corticosteroid Therapy of Septic Shock) trial showed no mortality benefit for patients with septic shock, ¹⁶⁴ the more recent APROCCHSS (Activated Protein C and Corticosteroids for Human Septic Shock) trial found a significant mortality benefit with no adverse effects. ¹⁶⁵ Likewise, in cases of severe infections like necrotizing fasciitis, corticosteroid administration has been suggested as a therapeutic means to reduce SIRS

and improve patient outcomes.¹⁴³ To date, although limited in patient number, a handful of prior studies have examined the benefits of corticosteroid administration in pediatric patients with septic arthritis.¹⁶⁶ Together, these studies suggest that as an adjunct to antibiotic administration, corticosteroids reduce patient pain, improve function of the infected joint at 12 months, reduce the number of days antibiotics are required, reduce the number of hospitalized days, and expedite the time to a normalized CRP.

Final Thought - Translation to Current Trends in Infectious Disease: APR in Covid-19 (Sars-Cov-2) Infections

Like MSKI, COVID-19 provokes a complex acute phase response that can be considered immunothrombotic, involving both the inflammatory and coagulation elements of the "survival" APR, culminating in the rapid onset of SIRS and SIC.167, 168 Together, SIRS and the developing coagulopathy result in a high rate of venous thromboembolism, microangiopathy, and subsequent fatal organ dysfunction, especially within the lungs. 169, 170 Interestingly, similar patterns within the "survival" APR can be observed between COVID-19 and disseminated MSKI (Table 5). Specifically, patients with severe COVID-19 develop low platelet counts with significantly elevated CRP values and concentrations of fibrin degradation products, each of which have been associated with length of ICU admission and mortality in these patients. 168, 171, 172 Furthermore, numerous studies have examined the prognostic capacity of NLR in patients with COVID-19. Liu et al. demonstrated that NLR was an independent risk factor for in-hospital mortality, such that for each unit increase in NLR, there was an 8% higher risk of mortality.¹⁷³ Much of the current COVID-19 literature assesses the role of either immune-mediated inflammation or thrombosis as a key driver of COVID-19-related disease, but there are clear pathologic implications for both survival inflammation and coagulation in this type of infection.

Table 5. MSKI and COVID-19 APR Similarities			
Acute Phase Reactants	 Elevated CRP, ferritin, D-dimer, and procalcitonin^{168, 172} Cytokine storm marked by high circulating levels of IL-6, IL-1 β, IL-8, 		
	and $\text{TNF}lpha^{178}$		
Cellular APR Components	High and low platelet counts, excess platelet activation ^{167, 171}		
	• High NLR ^{168, 173}		
	High level of macrophage/monocyte activation ¹⁷⁴		
	Platelet-leukocyte aggregates ^{174, 175}		
	Excess neutrophil activation and NETosis ^{169, 175}		

Further aligning with severe MSKI, studies assessing platelet and neutrophil function in COVID-19 patients suggest that this virus can hijack cellular components of the survival APR, causing a catastrophic systemic response that is difficult to treat.¹⁶⁸ Both platelets and neutrophils in COVID-19 patients are hyperreactive and easily form platelet-neutrophil aggregates (Table 2) which fuel rapid fibrin deposition and NET formation within major vessels and the microvasculature of organs. 174-176 Furthermore, overwhelming cytokine release from endothelial cells and leukocytes in COVID-19 infection triggers release of tissue factor from monocytes and activates the extrinsic coagulation pathway throughout the vasculature. 177 Post-mortem analysis of organs from patients with COVID-19 have demonstrated the presence of diffuse microthrombi rich in megakaryocytes, monocytes, platelets, fibrin, and NETs, regardless of anticoagulation. ¹⁷⁰ This suggests that excess thrombin is not the sole cause of fatal thrombosis and multiple organ dysfunction in these patients. Because of this, anticoagulation alone is unlikely to be effective in controlling this process, and recent studies have suggested that inhibition of both platelets and neutrophils may effectively improve outcomes in these patients. 169, 178 In summary, given the similar immunothrombotic responses involving both inflammation and coagulation, there are reciprocal lessons to be learned from treating patients with MSKI and patients with COVID-19.

Conclusion

Pediatric orthopaedic surgeons are commonly consulted for cases of suspected MSKIs. Unlike other emergent consultations, such as fracture care, MSKIs can present with marked heterogeneity in disease location, causative organism, disease severity, and required treatment. Given that time is often of the essence to promote optimal patient outcomes and reduce complication rates, there are four paramount tasks that all members of the medical and surgical team should set out to complete in cases of suspected pediatric MSKI.

The team should determine: 1) Where is the infection? 2) Is it an infection and if so, what is the pathogen? 3) How severe is the infection? 4) How to treat the infection? This review discussed the tools available to accomplish these four tasks in cases of pediatric MSKI, highlighting current best practices and recent medical advancements. Going forward, these tools should give treating physicians more confidence when evaluating patients with suspected MSKI. Though, physicians should be vigilant and never underestimate the pathogen, given that an exuberant APR can lead to SIC, SIRS, and patient complications. Important for current care, like MSKI, COVID-19 provokes a complex APR that can be considered immunothrombotic involving both the inflammatory and coagulation elements of the "survival" APR. By understanding the philosophy and tools discussed in this review, reciprocal lessons can be learned from treating patients with MSKI to patients with COVID-19.

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Additional Links

- https://posna2020.onlineeventpro.freeman.com/sessio ns/15335879/ondemand/25114770/Can-CRP-Predictthe-Need-to-Escalate-Care-After-Initial-Debridement-for-Musculoskeletal-Infection
- http://www.posnacademy.org/media/InfectionA++Hij acking+the+Acute+Phase+Response/0 mvsvk0nd/19 139942
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