Musculoskeletal Infection of the Hip

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Introduction

Musculoskeletal infection of the hip is a challenging disease process for orthopedic surgeons. Without rapid diagnosis and treatment, children may suffer from a wide range of devastating complications such as avascular necrosis of the proximal femoral epiphysis or even death. For these reasons, few consults in pediatric orthopaedics provoke more anxiety than the clinical presentation of a sick appearing child holding their hip in the flexed, abducted and externally rotated position (Fig. 10.1). Although the exact reasons are not known, anatomic characteristics of the bone, joint and muscles of the hip predispose it to be the most common site of infection in children [1]. Additionally, bacteria express virulence factors that promote tropism, or selectivity, for damaged and regenerating tissue [2]. As developing and regenerative tissue share many features (e.g. growth factors and angiogenesis), there is an increased prevalence of infection in children as compared to adults, even in the absence of injury [3]. In the modern era, the principle cause of morbidity and mortality results from the host response to the infection, referred to as the acute phase response [4–6]. While cases of isolated infections occur, infections that cause death and disability typically involve 'metastatic' disease, that is infections involving multiple tissues surrounding the hip (Fig. 10.2) [7–9]. As opposed to an isolated trauma, the acute phase response in metastatic infection is significantly more exuberant because of the amount of tissue injured, the dura-

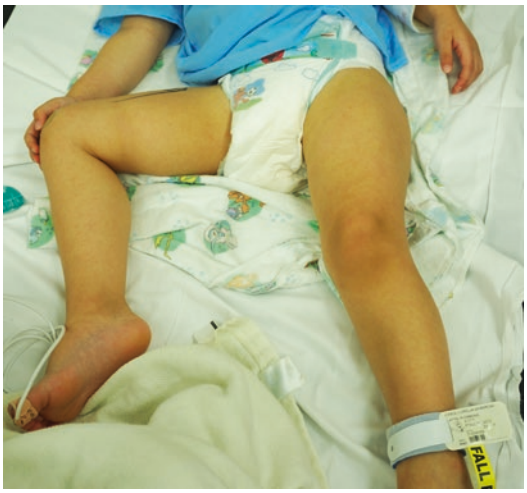

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Fig. 10.1 Warning signs. Exam findings of a flexed externally rotated and abducted hip is the most concerning for infection around the hip in children

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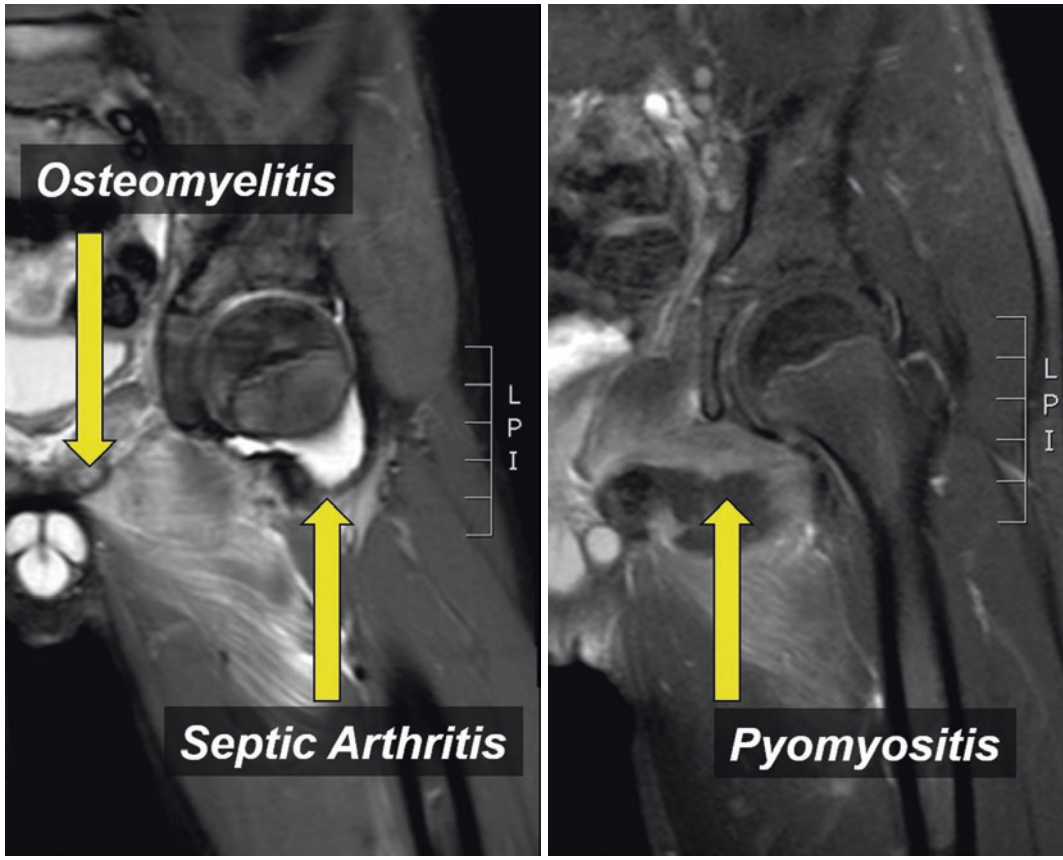

Fig. 10.2 Involvement of multiple tissues. Most severe cases of musculoskeletal infection of the hip do not involve an isolated tissue type. In these MRI cuts, there is evidence of both pyomyositis and osteomyelitis in addition to septic arthritis in the same patient. This is typical of cases of hip infections where pathogens rarely stay isolated to the joint

tion of the injury, as well as pathogen 'hijacking' of acute phase reactants. This dysregulated acute phase response—specifically, pathologic activation of inflammation and coagulation—provokes predominately-thrombotic complications including death, septic pulmonary emboli, and deep venous thrombosis [6]. In addition, given the essential role of the vasculature in the developing hip, thrombosis associated with a dysregulated acute phase response can lead to avascular necrosis of the epiphysis and metaphysis; potentially resulting in loss of joint function and normal limb development. Unfortunately, clinical features of hip infection are often indistinguishable from trauma, neoplasm and rheumatologic conditions. In addition, current culturing techniques are inefficient relative to the required rapid clinical decision making to avoid complications [10]. Fortunately, modern techniques of monitoring the acute phase response and utilizing improved imaging modalities permit rapid diagnosis, risk assessment and monitoring of efficacious antibiotic and surgical treatment. Thus, the role of the orthopaedic surgeon in caring for patients with peri-hip infection should focus on (1) making a rapid diagnosis (2) treating with appropriate antibiotics and debridement when necessary (3) preventing an exuberant or prolonged acute phase response and (4) avoiding avascular necrosis of the proximal femoral epiphysis.

"A dysregulated acute phase response—specifically, pathologic activation of inflammation and coagulation—provokes predominately-thrombotic complications including death, septic pulmonary emboli, and deep venous thrombosis in children with aggressive musculoskeletal infections".

Pathophysiology

Anatomic Features that Support Hip Infection

The most common route of hip infection is hematogenous. Hematogenous osteomyelitis has a strong predilection for the most rapidly growing end of the large long bones, especially those of the lower extremity. Patients with a compromised immune response, such as the neonate, a malnourished child or a preceding viral infection, such as varicella, are known to be susceptible to infection [11, 12]. However, even immune competent children can develop spontaneous infection of the hip. As a result, many have speculated on the unique characteristics of the developing musculoskeletal system that contribute to susceptibility of infection (Fig. 10.3). The pathophysiology of osteomyelitis in the developing child is thought occur because of the unique vascular anatomy of the physis in conjunction with its relatively 'immune privileged' nature. For example, the tortuous anatomy of the vasculature of the zone of ossification in the metaphysis has been demonstrated to cause turbulent blood flow permitting bacterial accumulations [13]. Additionally, developing bone produces factors that inhibit innate immune cell activity in the metaphysis, but not the diaphysis [14]. During an infectious process, the immune privileged state is lost to fight the infection, which results in robust macrophage, or osteoclastic, resorption of bone, providing the characteristic lucent findings of osteomyelitis on radiographs.

Anatomic features of the hip also contribute to the association of proximal femoral osteomyelitis with septic arthritis. For example, the metaphysis of the proximal femur lies within the joint, providing a direct inoculum when infected (Fig. 10.4). Additionally, following dissection of cadaveric specimens, it was speculated by Ogden and Trueta [15, 16] that patients younger than 18 months have a transphyseal blood supply to the chondroepiphysis, which predisposes infants to develop osteomyelitis and septic arthritis. However, in reviewing these studies, the representation of the size, anatomic location, persistence and pathophysiologic contribution of these vessels is likely overstated. Ogden's graphic representation of this vasculature in his 1974 publication is an inaccurate, and often reproduced, representation of these vessels [15]. Specifically, both Ogden and Trueta

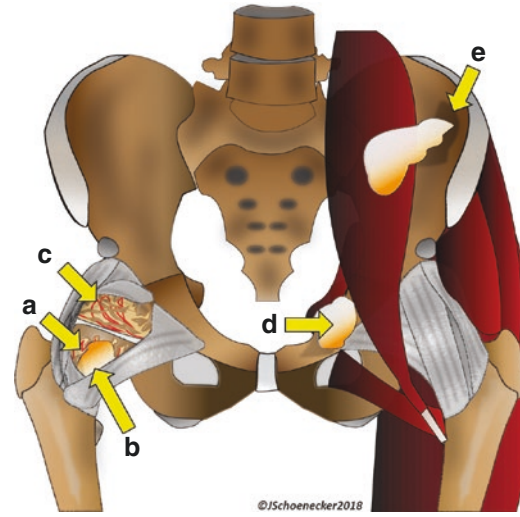

Fig. 10.3 Pathophysiology of hip infection. (**a**) The femoral head and neck have a torturous blood supply with immune privilege, predisposing it to hematogenous infection. (**b**) The metaphysis of the proximal femur is intracapsular, so that osteomyelitis of the area also frequently leads to septic arthritis of the hip. (**c**) The blood supply to the epiphysis is tenuous so infection of the hip puts the epiphyseal vasculature at risk, making avascular necrosis a significant concern. (**d**) Pyomyositis is a common element of hip infections including in the obturator internus muscle as in Fig. 10.2. Although muscle is usually resistant to infection, many cases of pyomyositis start as osteomyelitis that then erupts into the muscle. (**e**) Pyomyositis can also commonly occur in the psoas muscle as in Fig. 10.9

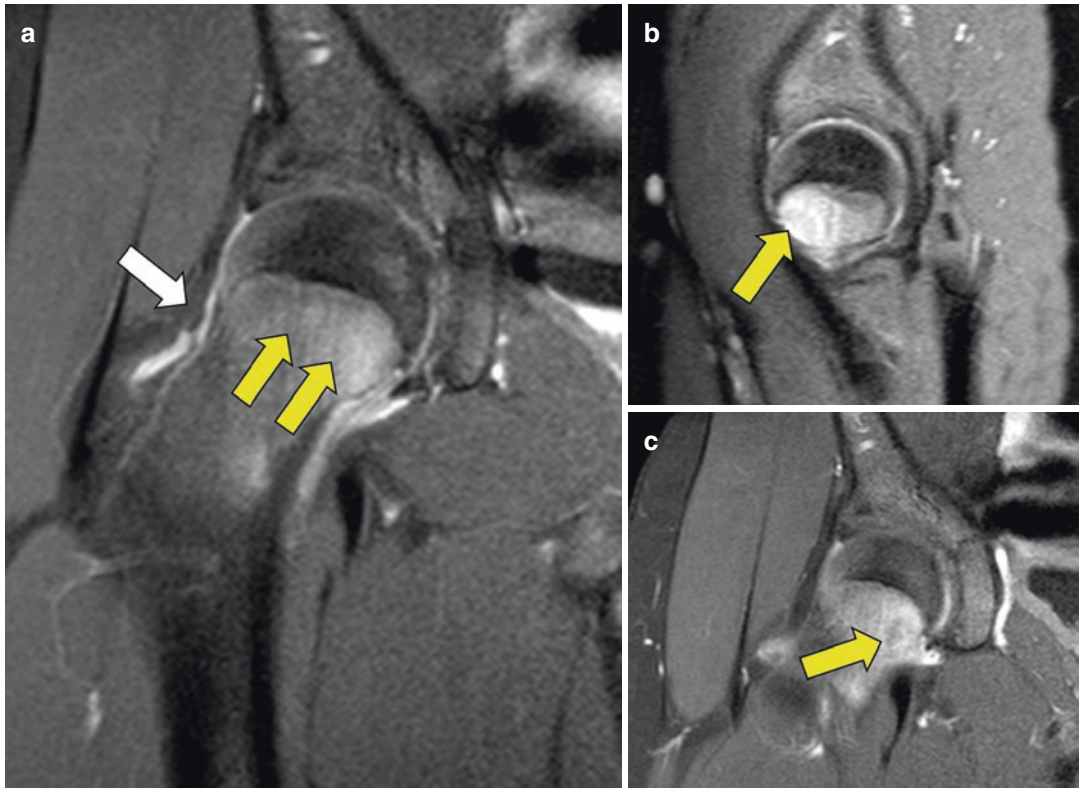

Fig. 10.4 Intracapsular osteomyelitis and septic arthritis. (**a**) A coronal MRI shows osteomyelitis of the femoral metaphysis spreading into the femoral head (yellow arrows). The white arrow points to the hip capsule, which shows that the infection is intracapsular. (**b**) Sagittal MRI demonstrates the infection of the femoral neck (yellow arrow). (**c**) The yellow arrow points to the infected femoral neck once again, this time with the infection breaking out of the cortex and involving the hip joint itself causing septic arthritis

found a few small transphyseal vessels at the far lateral physis in children who died from overwhelming sepsis. These patients had histologic signs of avascular necrosis, a condition which Trueta later proved to cause the development of transphyseal vascularization and bar formation. A thorough search of the literature has not identified any studies in developing humans, or other mammals [17] that support this speculation. More commonly, the epiphysis is less susceptible to infection from the metaphysis, as the physis acts as a barrier to intraosseous blood flow between the metaphysis and the epiphysis.

The precise pathophysiology by which septic arthritis occurs is less well understood than for osteomyelitis. Historically, skeletal muscle was thought to be inherently resistant to bacterial infection. However, given the recent increase in reports of pyomyositis, especially around the hip [18], there are unknown features of skeletal muscle that permit bacterial invasion. Given that pyomyositis is commonly contiguous with osteomyelitis, it is likely often caused by an extension from a breached subperiosteal abscess (Figs. 10.2 and 10.3).

"The pathophysiology of osteomyelitis in the developing child is thought occur because of the unique vascular anatomy of the physis in conjunction with its relatively 'immune privileged' nature. Additionally, the metaphysis of the proximal femur lies within the joint, providing a direct inoculum to the joint from osteomyelitis".

Anatomic Features Leading to Permanent Deformity of the Proximal Femur

The activation of the acute phase response and the 'hijacking' by pathogens (see below) can contribute to a devastating sequelae of musculoskeletal hip infection, namely avascular necrosis of the femoral head. The blood supply of the pediatric femur is tenuous. Because the avascular physis prevents intramedullary blood flow directly to the femoral head epiphysis from the proximal femur, the blood must course in an extramedullary path. The main vessels that supply the femoral head are derived from the medial circumflex femoral artery. It gives off the posterosuperior lateral epiphyseal branch and the posteroinferior retinacular branch. The lateral circumflex artery also provides some vascular flow, but regresses throughout childhood. While the ligamentum teres does have some small arteries within it, it does not provide any effective supply to the femoral head. Compromise of the medial circumflex artery, or its smaller retinacular and epiphyseal branches, can lead to avascular necrosis and eventual collapse or deformity. Unfortunately, the hyper-thrombotic state of musculoskeletal infection leads to thrombotic and embolic events that can impair this delicate blood supply (Fig. 10.5). Additionally, there is concern that increased pressure within the hip capsule generated by the infection can deprive the femoral head of its necessary blood supply [19, 20]. For this reason, hips should not be immobilized in an extended position, but patients should be left in whatever position is comfortable for them.

Avascular necrosis has several potentially devastating consequences (Fig. 10.5). Collapse of the femoral head leads to incongruity between the head and the acetabulum and subsequently causes early arthritis through increased friction within the joint. While procedures do exist to help reshape the femoral head, many patients will require early arthroplasty. Additionally, Trueta

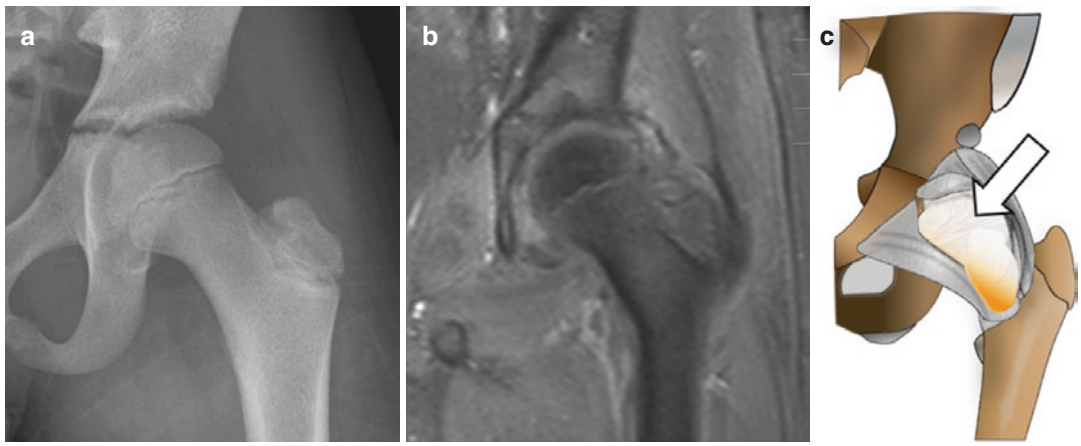

Fig. 10.5 Complications of hip infection case example. A 9-year-old boy presented with 1-week of hip and groin pain who developed fever and shortness of breath. He was admitted to the ICU with concern for septic arthritis of the left hip, cavitary pulmonary lesions and a left iliac DVT, suggesting advanced infection. (**a**) Radiographs showed no pathology at presentation. (**b**) However, MRI showed extensive edema in the pericapsular muscles with effusion. (**c**) This diagram shows location of the infection of the pericapsular muscles and joint. He underwent irrigation and debridement with pressurized purulent fluid released from the hip joint that was positive for MSSA. (**d**) Bone scan at the time shows decreased perfusion of the femoral head. He underwent repeat debridement and drilling of the pelvis and proximal femur. (**e**) Impaired effusion of the femoral head secondary to infection leads to necrosis. (**f**) Due to avascular weakening of the femoral head and neck, there was a slip of the capital epiphysis as shown on MRI with a fully avascular femoral head. (**g**) Diagram showing slipped capital femoral epiphysis with avascular necrosis. (**h**) Radiographs again demonstrate slipped epiphysis with early bone resorption. (**i**) Several months later, the femoral head had completely resorbed

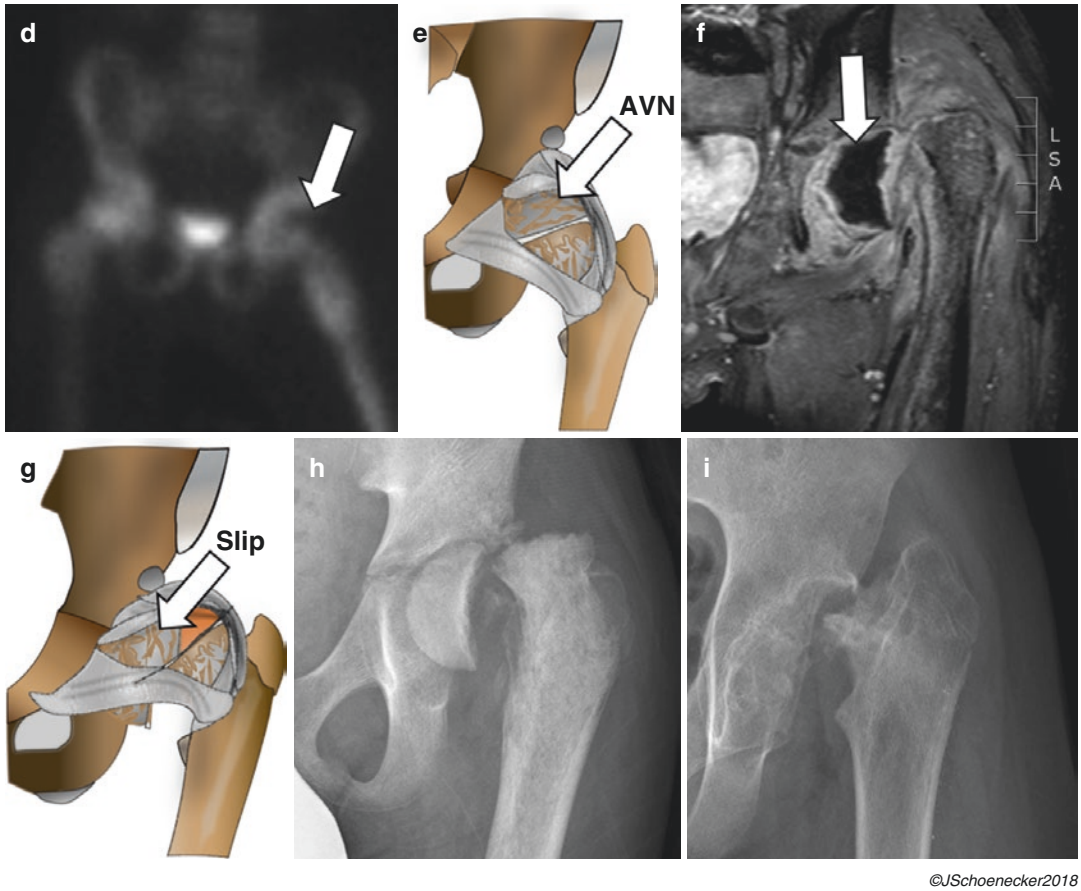

Fig. 10.5 (continued)

[21] demonstrated that avascular necrosis of the epiphysis leads physeal bar formation because of transphyseal revascularization of the epiphysis. This leads to growth arrest, deformity of the femoral head, and incongruity of the joint like cases of femoral head collapse. Additionally, hypoxia of the femoral head may lead to chondrolysis of its articular surface, again advancing arthritis and making early arthroplasty necessary. While the articular cartilage can survive in a relatively hypoxic environment, it cannot survive the ischemic conditions of osteonecrosis. In severe cases, such as this case of septic arthritis, osteomyelitis, and pyomyositis, the entire femoral head can be resorbed following infection.

"Compromise of the medial circumflex artery or its smaller retinacular and epiphyseal branches, can lead to avascular necrosis and eventual collapse or deformity".

Acute Phase Response: The Double-Edged Sword

Damage to musculoskeletal tissue initiates a cascade of reactions that is collectively referred to as the acute phase response. Through coagulation, inflammation, and regenerative processes, this physiologic response has an impact on virtually

every organ system. The response typically occurs over six weeks following an isolated injury, such as trauma or elective surgery (Fig. 10.6) [6, 22]. In the ideal setting, the acute phase response to injury occurs in relatively discrete stages. First, in the 'survival' phase coagulation and inflammation forms a rudimentary compartmentalization of the injury which serves to provide hemostasis and fight infection. Second, during the 'reparative phase', inflammatory cells change to initiate repair removing the damaged tissue and temporary fibrin/platelet sealant and initiate revascularization, tissue proliferation, and a return to native anatomy. The failure to proceed from one phase to the next prohibits normal tissue healing and recovery. For example, the failure to remove the coagulation matrix protein fibrin prevents angiogenesis and fracture repair [23, 24].

A balanced acute phase response is critical for human survival and recovery from injury. An insufficient response may be observed in patients with cirrhosis, as the liver is its principal effector organ [6]. Following injury these patients may experience hemorrhage, infection, and impaired tissue regeneration. On the other hand, an excessive or prolonged acute phase response (Fig. 10.7) is a major cause of systemic complications observed in orthopaedics. A prolonged 'survival' phase portends the development of systemic inflammatory response syndrome (SIRS) with a concomitant coagulopathy, which ignorantly increases the risk of vascular thrombosis [25]. Additionally, the prolonged survival phase causes a delay, and potential failure of the reparative phase, leading to chronic non-healing wounds [23, 24].

In the setting of infection, this dynamic and coordinated progression of the acute phase response is lost ([2, 6]). When infectious pathogens invade the body, bacterial proliferation and

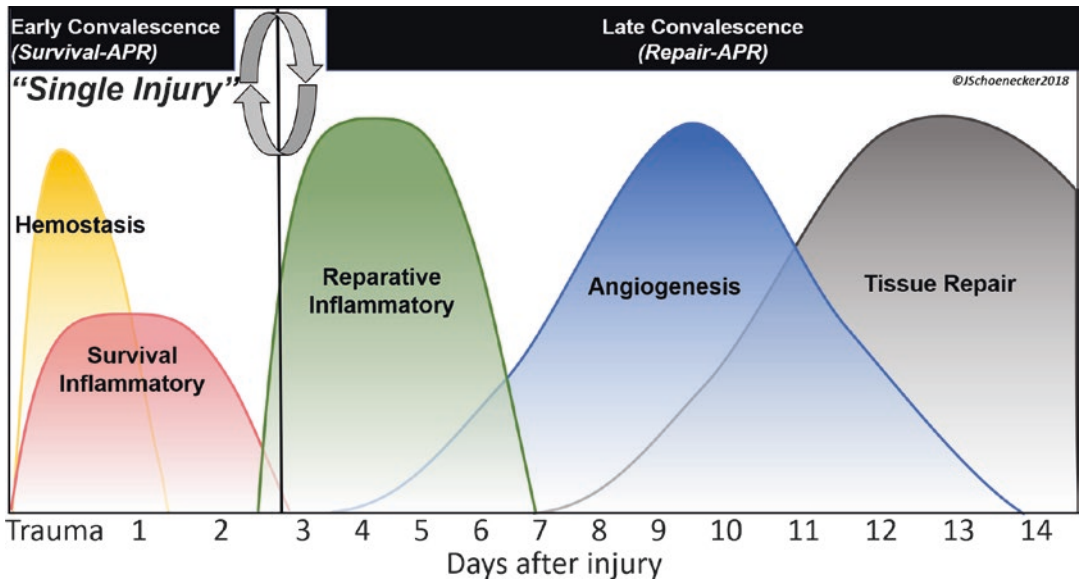

Fig. 10.6 The acute phase response. The body's response to infection or any other injury includes the acute phase response, which has two phases. The first is early convalescence or survival that contains the injury utilizing coagulation and inflammation to achieve hemostasis and prevent or eliminate infection, enabling survival and transition to the late convalescence or repair phase. This phase aims to recreate functional anatomy by eliminating scar and abscess tissue. It includes angiogenesis to revascularize structures and repair of damaged tissues. Understanding these ordered and distinct 'survival' and 'repair' phases determines when and how clinicians should intervene

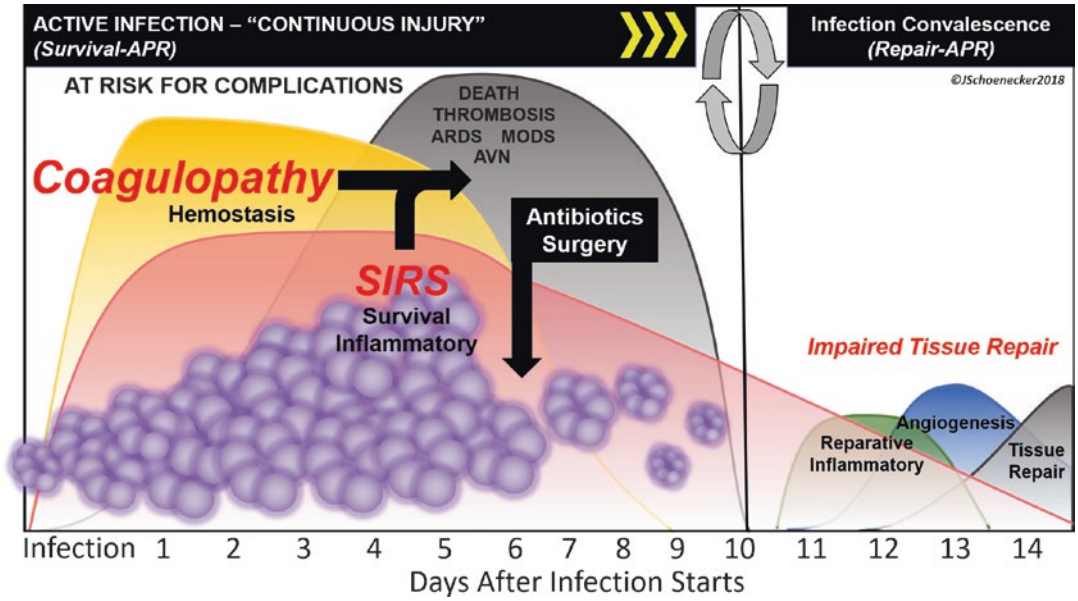

Fig. 10.7 Acute phase response to infection. In infection as in other injuries, the acute phase response is essential. However, it can also lead to complications. Excessive coagulation and inflammatory response can lead to thrombotic complications, organ failure, AVN, and even death. An acute phase response that is both very exuberant and long lasting puts the body at especially high risk for these complications. However, inadequate acute phase response will not eliminate the infectious threat to survival. Antibiotics and surgery are often necessary to end the injury and help the body fight infection and enable convalescence and repair

virulence factor expression cause damage to surrounding tissues. Additionally, as described above, bacteria 'hijack' many of the acute phase reactants, exacerbating the survival response. Injury caused by a developing infection persists until it is resolved by the immune system, antibiotics, and/or surgical debridement, making the infection induced acute phase response dramatically more exuberant than elective surgery or trauma. Musculoskeletal infection may be considered continuous activation of the survival phase of the acute phase response, only halted by initiation of antibiotic therapy or surgical debridement [6]. This continuous activation leads to overwhelming SIRS and a consumptive coagulopathy accounting for most of the morbidity and mortality observed in these patients. In addition to complications such as respiratory failure from SIRS, vascular thrombosis leads to thromboembolism, and death [6]. Furthermore, this response causes thrombosis of bone. In the epiphysis, thrombosis associated with septic arthritis or osteomyelitis may cause chondrolysis, joint resorption and physeal arrest. In the metaphysis and diaphysis thrombosis leads to sequestration, which if unresolved by involucrum, can lead to pathologic fracture and other abnormalities. Therefore, the acute phase response may be viewed as a 'double-edged sword', with a well-coordinated acute phase response being essential for survival and recovery from injury, but an excessive response leading to devastating complications [6]. Together, these concepts present a paradox for surgeons and health care providers caring for these patients. Many of the elements of the acute phase response are essential to combat and eliminate developing infections. However, in the process, this response may lead to many of the complications observed in patients suffering from infected musculoskeletal tissue (Fig. 10.7).

"The acute phase response may be viewed as a 'double-edged sword', with a well-coordinated acute phase response being essential for survival and recovery from injury, but an excessive response leading to devastating complications".

Bacterial Hijacking of the Acute Phase Response

Pathogenic bacteria possess virulence factors that allow them to invade, persist, and disseminate within the human body [2]. Bacteria travel through the circulatory and musculoskeletal systems daily and yet rarely cause clinical infection. Although random chance may have a role in determining where and when bone and joint infection occurs, specific patterns of infection have been observed that can lead to no other conclusion except that trauma is the main predisposing factor contributing to 'spontaneous' hip infection [26, 27].

Unfortunately, as part of millions of years of co-evolution, bacteria have developed sophisticated mechanisms to hijack the acute phase response (see pathophysiology below for more detail regarding the acute phase response). The coagulation system serves as one of the initial defense mechanisms against bacterial invasion by immobilizing bacteria within clots and recruiting leukocytes to the site of infection through integrin expression on fibrin [2]. However, bacteria like S. aureus have come to use this system to their advantage. The most well-known of the S. aureus virulence factors is coagulase (Coa), which is secreted into the extracellular environment and activates prothrombin to thrombin [2]. This Coa-thrombin complex then catalyzes the cleavage of fibrinogen to fibrin, which surrounds the bacteria and forms a protective abscess, necessitating surgical intervention or drain placement to clear infection.

Many additional bacteria that cause musculoskeletal infection similarly express virulence factors that have been adapted to hijack the acute phase response to their advantage. Unsurprisingly, many bacteria have developed virulence factors that manipulate the fibrinolytic system to avoid being trapped by pro-coagulant factors. S. pyogenes, for example, produces streptokinase, which binds and activates plasminogen far more effectively than the body's normal pathway for activation of fibrinolysis [2]. The bacteria then use the activated plasmin to cleave fibrin clots, laminin basement membranes, and DNA nets. Other bacteria that target plasmin include S. aureus, E. coli, B. burgdorferi, N. meningitidis, and P. aeruginosa, helping them to disseminate throughout the body [2]. These virulence factors help explain why the bacteria that typically cause musculoskeletal infections often disseminate amongst various anatomical compartments.

This interaction between the host's acute phase response and infection pathogenesis is an evolutionary battle that continues to the present day. Importantly, not only do virulence factors differ significantly between differing species of bacteria (e.g. Staphylococcus aureus compared to Kingella kingae), but virulence factors rapidly change within a species. Therefore, the extent by which a specific bacterium drives tissue injury and the acute phase response is dependent on the genetic composition of the bacterium. Nevertheless, awareness of the interplay between the acute phase response and bacterial infection will aid in the diagnosis, prognostication, and treatment of musculoskeletal infections [2, 6].

Key Aspects of the Infection Provoked Acute Phase Response

1. The acute phase response is the physiologic reaction to tissue injury, such as musculoskeletal infection, trauma, and orthopedic surgery.
2. While trauma and orthopedic surgery are temporally isolated injuries, musculoskeletal infection is continuous and leads to an exuberant activation of the acute phase response. The response continues until the infection is resolved.
3. The acute phase response to musculoskeletal infection is paradoxical as it is not only necessary for the resolution of infection, but also responsible for many of its associated complications.
4. Given the interplay between musculoskeletal infection and the acute phase response, measuring positive and negatively regulated acute phase reactants has been useful in diagnosing and monitoring patients with musculoskeletal infection.

5. Future strategies that modulate the acute phase response have the potential to improve treatment and prevent complications associated with musculoskeletal infection.

Natural History

The natural history of untreated hip infection is devastating. Only recently in orthopaedics has the burden and mortality of musculoskeletal infection been surpassed by other pathologies. In the pre-antibiotic and pre-vaccine era, the mortality rate of acute hematogenous osteomyelitis in children was about 50%, due to dysregulated acute phase responses caused by overwhelming sepsis and metastatic abscesses [28, 29]. The advent of antibiotics, vaccines and the capacity to perform effective debridement of infected tissue has tremendously affected the outcome of these patients, and the mortality rates from pediatric musculoskeletal infection have dropped significantly. With modern treatment as mentioned above, morbidity and mortality has become far lower [3, 9, 30]. In most cases, children present with pain and refusal to bear weight, possibly with constitutional symptoms such as fever and malaise. Without treatment these symptoms would frequently progress to sepsis, shock, and death. Even if the child survived, they would be at risk for growth deformities and avascular necrosis of the hip (Fig. 10.5). With the advent of antibiotics and effective surgical debridement, these sequelae are uncommon. With effective treatment of musculoskeletal infection of the hip, improvement should be rapid. The combination of surgical debridement if necessary and intravenous antibiotics should lead to rapid improvement in symptoms and inflammatory markers within the first several days.

Patients should quickly improve after debridement and antibiotic treatment for septic arthritis or pyomyositis. Osteomyelitis requires a longer treatment period, but again improvement in laboratory markers and patient symptoms should occur quickly with effective treatment. Further on in the chapter, a contrasting case of hip infection that did receive early treatment and required multiple debridements is presented.

"In the pre-antibiotic and pre-vaccine era, the mortality rate of acute hematogenous osteomyelitis in children was about 50%, due to dysregulated acute phase responses caused by overwhelming sepsis and metastatic abscesses".

Epidemiology

Pyogenic organisms are the most common causative organisms. Staphylococcus aureus remains the most common causative organism, occurring in 40–90% of cases of musculoskeletal infection [29, 31]. Since the development of routine vaccinations of infants against Haemophilus influenza, the incidence of musculoskeletal infection caused by H. influenza has dramatically decreased [32]. Other organisms commonly causing osteomyelitis or septic arthritis include coagulase-negative Staphylococcus, group A β-hemolytic Streptococcus, Streptococcus pneumoniae, and group B Streptococcus [1]. Kingella kingae is now recognized as the most common organism responsible for septic arthritis in children younger than 24 months [33].

"Kingella kingae is now recognized as the most common organism responsible for septic arthritis in children younger than 24 months".

The epidemiologic patterns of musculoskeletal infection are continually changing owing to mutations in the bacterial genome, vaccinations and antibiotics. Osteomyelitis worldwide incidence estimates range from 1 in 1000 to 1 in 20,000 [34–36], and half of all cases of osteomyelitis occur in children younger than age 5 [30, 37]. In childhood, septic arthritis occurs about twice as often as osteomyelitis and tends to have its peak incidence in the early years of the first decade [30]. Because of increased use of MRI

and awareness, pyomyositis, once thought to be a 'tropical' infection, is being reported with increased frequency in developed countries and commonly affects the musculature about the hip. For example, at Vanderbilt Children's Hospital, pyomyositis was diagnosed at a ratio of 2:1 to septic arthritis in children consulted for 'rule out' hip infection [18].

Most Common Organisms in Pediatric Hip Infections

1. Staphylococcus aureus
2. Kingella kingae
3. Streptococcus group A β-hemolytic, pneumoniae and group B

Clinical Presentation

General Presentation

Pain is the most common symptom in patients with a hip infection. Children may refuse to walk, refuse to bear weight, limp, or refuse to use or move a limb. They most often hold their hips in a flexed, abducted and externally rotated position (Fig. 10.1). A history of recent or concurrent illness is important information to consider when evaluating a patient for possible hip infection. Recent upper respiratory symptoms may suggest a noninfectious cause for patient symptoms such as toxic synovitis or poststreptococcal reactive arthritis (PSRA) [38]. Patients with musculoskeletal infection frequently present with a history of local trauma. Signs and symptoms of acute bacterial infection, trauma and cancer around the hip are very similar and are discussed in more detail below. Inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), should be used along with the white cell count as non-specific but sensitive (especially the CRP) tests for infection. Traditionally, the 'Kocher Criteria' [39] have been used to help distinguish septic arthritis of the hip from other conditions, like transient synovitis. Recent studies have shown that these diagnostic criteria are unable to distinguish septic arthritis from osteomyelitis or pyomyositis. Additionally, many infections around the hip are not isolated to one specific anatomic location, but most often is a combination of conditions that occur in contiguous areas around the hip. While US can be helpful at demonstrating a hip effusion (Fig. 10.8), it cannot provide information about the presence of

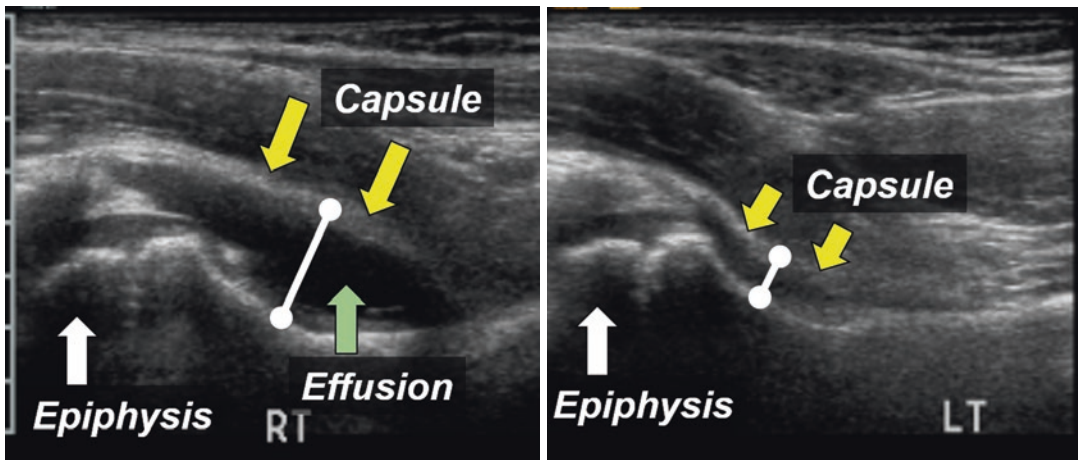

Fig. 10.8 Ultrasound in hip infection. Ultrasound is an effective imaging method for identifying hip effusion as you can see the capsule elevated from the proximal femur with increased fluid in the joint. However, it is not specific for infection and does not show additional sites of infection

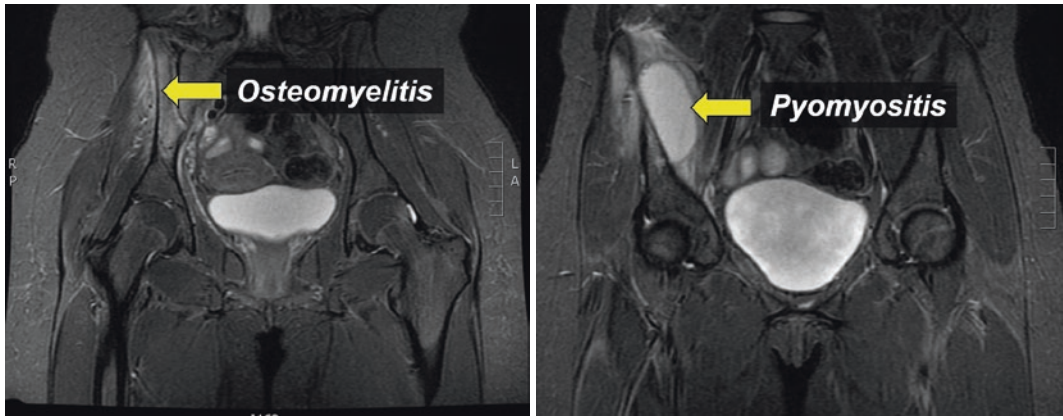

Fig. 10.9 Magnetic resonance imaging. MRI is the best imaging modality for hip infections because it can show both the hip effusion demonstrated with ultrasound and additional infection as seen here with pyomyositis of the psoas and osteomyelitis of the ilium

osteomyelitis of the proximal femur or pelvis, or pericapsular pyomyositis. Therefore, the authors contend that MRI (Fig. 10.9) is the best imaging modality to diagnose infection around the hip.

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Osteomyelitis

Children with osteomyelitis present with similar signs and symptoms as those with septic arthritis, however, they usually lack the joint irritability that is found in children with septic arthritis. They will usually exhibit tenderness to palpation of the affected area instead. Historically, it is often not possible to identify a causative organism in a substantial percentage of patients with osteomyelitis and therefore the diagnosis is defined as being definite, probable, or likely [40]. Definite osteomyelitis is present when an organism is recovered from bone or adjacent soft tissue or when there is histologic evidence of infection. Osteomyelitis is probable when there is a positive blood culture in addition to clinical and radiographic features of osteomyelitis, and osteomyelitis is likely to be present when there are typical clinical and radiographic features of osteomyelitis along with a response to antibiotics in the absence of a positive culture.

Septic Arthritis

An even higher percentage of patients with septic arthritis have negative cultures. The gold standard for diagnosis of septic arthritis is obtaining a sample of joint fluid for cell count, gram stain and culture. This can either be done under sedation in the emergency room, with interventional radiology, or in the operating room under general anesthesia. A nucleated cell count of greater than 50,000 cells/mL and >75% segmented neutrophils and/or the presence of a positive gram stain/culture is generally considered to be positive for septic arthritis. In cases where the cell count is inconclusive (10,000–75,000 cells/mL) the decision to perform an arthrotomy depends on the preference of the treating physician.

> ***"A nucleated cell count of greater than 50,000 cells/mL and >75% segmented neutrophils and/or the presence of a positive gram stain/culture [on synovial fluid analysis] is generally considered to be positive for septic arthritis".***

Pyomyositis

Pyomyositis in children is most common around the hip joint (pericapsular pyomyositis). Children with this type of infection present similarly to those with septic arthritis, including joint irritability and limited range of motion (ROM). Clinical examination and laboratory markers often fail to distinguish this type of infection from septic arthritis and osteomyelitis. MRI is the only imaging modality that adequately diagnoses pyomyositis, as it is not able to be seen on XR or US examinations. Recent studies have shown that pericapsular pyomyositis is twice as common as septic arthritis of the hip. In many institutions, there is not wide availability of MRI, especially if the child is young enough to need sedation. When this is the case, FAST-sequence MRI is effective at diagnosing pericapsular pyomyositis, as well as other foci of infection. The protocol is a non-contrasted, non-sedated study that can be done in less than 30 min. It provides a coronal short T1 inversion recovery (STIR) sequence and an axial T2 sequence.

Essential Clinical Tests

Rapid Diagnosis of Hip Infection in Children:

1. *Examine*: Children hold their hip in a flexed, abducted and externally rotated position that increases capsular volume (Fig. 10.1). Older children refuse to bear weight on their affected leg.
2. *Measure*: The most efficient two measures of the acute phase response are temperature and CRP (Fig. 10.13).
3. *Image*: The most comprehensive measure of septic arthritis, osteomyelitis and pyomyositis is MRI (Fig. 10.9).
4. *Aspirate*: Aspiration is often essential to determine if the joint is involved (Fig. 10.12).

Differential Diagnosis

Trauma, neoplasm and rheumatologic conditions may present with characteristics like hip infection. Similar features are typically present, including pain, tenderness, swelling, and soft-tissue swelling on radiographs. However, several distinguishing features may be present. Traumatic symptoms are usually sudden in onset with gradual improvement, compared to symptoms of infection, which are more likely to be gradual in onset and progressive in nature. The most common malignancy in children is leukemia, which presents with diffuse bone pain, anemia and bleeding [41], is less likely to be focal to the hip. Additionally, children with leukemia often present with radiographic findings, such as lucent metaphyseal bands [42]. In the young child, metastatic neuroblastoma or eosinophilic granuloma should be considered. Older children are more likely to have Ewing or osteogenic sarcoma. Lymphoma may also occasionally arise primarily from bone. These lesions should be approached as a malignancy with complete staging studies and diagnosis confirmed by biopsy using an approach that will not jeopardize limb salvage surgery. The adage "culture the tumor and biopsy the infection" is wise advice to follow.

Other post-infectious or rheumatologic conditions may also confound the diagnosis of septic arthritis. One of the most difficult and yet important differentials is between septic arthritis of the hip and toxic synovitis, a condition thought to be a post infectious arthritis. The physical signs are similar in both, with limited and painful internal rotation, abduction, and extension, however, the pain is usually worse in septic arthritis. A longer history of symptoms, with cyclic improvement and worsening, suggests toxic synovitis. A sequela of group A streptococcal infection, rheumatic fever most often causes pain in the knees and ankles but can involve the hip. It is typically considered transitory and migratory. Diagnosis of rheumatic fever is based on the Jones criteria [38]. For patients who have a documented history of recent group A Streptococcus exposure, do not meet the Jones criteria, but have significant arthralgia without other identifiable cause,

the diagnosis of post-streptococcal reactive arthritis (PSRA) has been used [43, 44]. A recent streptococcal infection may be documented by the presence of an antibody response to group A Streptococcus or positive throat culture. Patients with acute rheumatic fever are treated with long-term prophylactic antibiotics to prevent recurrent rheumatic fever and associated carditis. The risk of carditis to children with PSRA is unclear but felt to be low, and the role of long-term prophylactic antibiotics following PSRA is controversial but not typically recommended. Although the hip joint can be affected in juvenile idiopathic arthritis (JIA), it is rarely the initial joint involved. JIA should be considered in the less straightforward cases of 'rule-out' septic arthritis. Symptoms in JIA are typically more gradual in onset than septic arthritis, and the patient usually remains ambulatory. Additionally, a joint affected by JIA typically looks worse on X-ray than it functions.

"Trauma, neoplasm and rheumatologic conditions may present with characteristics like hip infection".

Imaging

Imaging most commonly begins with standard radiographs. The greatest utility of radiographs is to identify mimicry of infection such as tumor or trauma (Fig. 10.10). In addition, infection may be suggested by findings such as soft-tissue swelling or asymmetry of the hip joints, indicating an

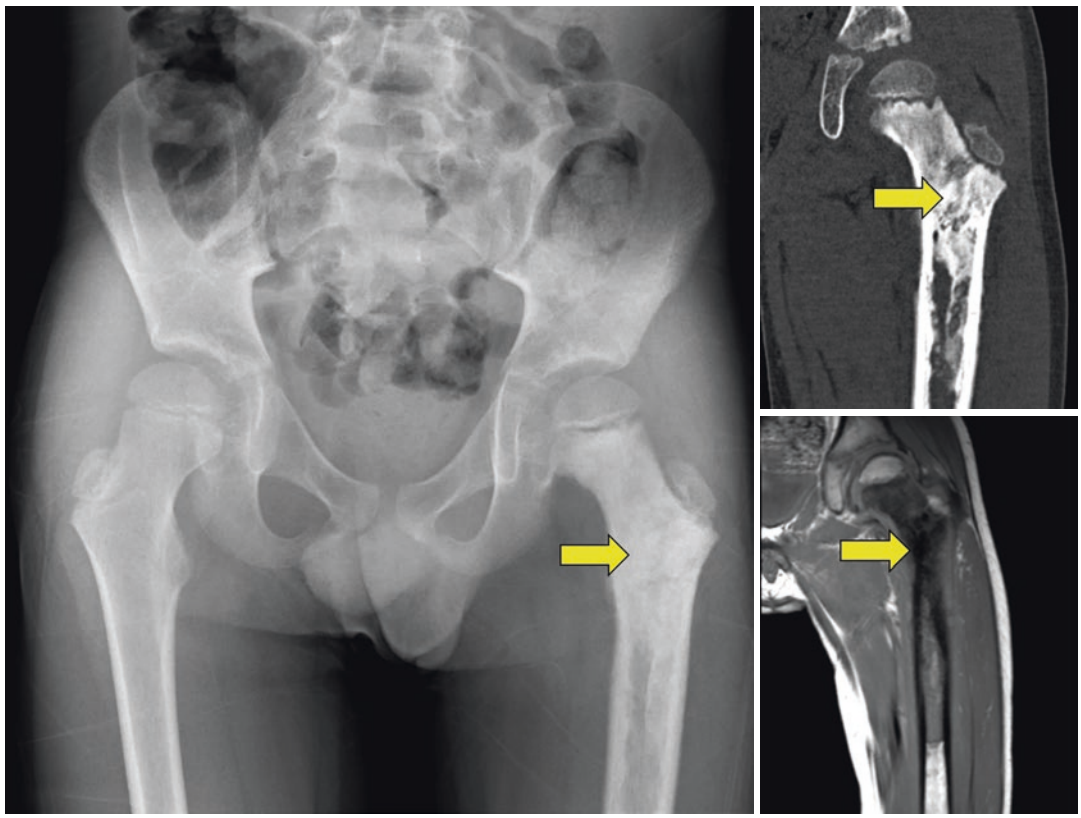

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Fig. 10.10 Radiography in hip infection. The main role of radiographs in hip infection is ruling out other pathology, such as fracture, or in this case malignancy, as children often present with hip pain and refusal to bear weight in cases of cancer of the hip as well. This 6-year old presented with hip pain and was found to have osteosarcoma of the proximal femur (indicated by yellow arrow)

effusion. The time required before bone changes become visible on plain radiographs is at the earliest 7 days, typically after the child presents, and is therefore unreliable. In addition to radiographs, standard work up includes ultrasound to identify a hip effusion. Although, not specific, identification of a hip effusion often guides treatment by suggesting the need of a hip aspiration. Because of the rapid progression of effusions, false negatives can occur if a child presents early in their course, and repeat ultrasound, or MRI should always be considered in a child whose symptoms fail to improve or worsen. MRI is an increasingly valuable imaging tool used to evaluate musculoskeletal infection, especially as rapid MRI without sedation is becoming more available. MRI provides better soft-tissue resolution and can be used to identify hip effusion, osteomyelitis and pyomyositis. The utility of MRI is underscored by the implementation of MRI in evaluation of suspected septic arthritis, at our institution where we determined a diagnosis of peri-capsular pyomyositis at a rate of 2:1 to septic arthritis [18]. These findings have significantly changed our approach to the work up of septic arthritis.

In cases where there is a hip effusion present, or there is concern for septic arthritis, the authors strongly advocate MRI (Fig. 10.9). Not only does MRI help to identify any contiguous areas of infection, it can direct the approach for aspiration of the hip joint. Hip aspiration is commonly performed through a medial approach just posterior to the adductor tendon. A large percentage of cases of pyomyositis around the hip affect the adductor compartment. Therefore, there is a theoretical risk of contaminating the hip joint if the hip is aspirated through the medial approach in these cases. In many institutions, there is not wide availability of MRI, especially if the child is young enough to need sedation. When this is the case, FAST-sequence MRI is effective at diagnosing infection around the hip joint. When MRI cannot be obtained in a timely manner, however, and there is sufficient concern for septic arthritis based on clinical exam and effusion on US, treatment should not be delayed to obtain advanced imaging.

Essential Imaging

- Imaging
  - Radiographs (Fig. 10.10)
    - Help to rule out tumor or fracture
    - Often negative in acute infection
    - Can show evidence of osteomyelitis
  - Ultrasound (Fig. 10.8)
    - Effusion is suggestive of infection, but very common in transient synovitis
    - Large effusions are more likely to be septic arthritis [18]
  - MRI (Fig. 10.9)
    - Gold standard in identifying hip infections
    - FAST sequence MRI is helpful in identifying location of infection, especially pericapsular pyomyositis
    - STIR sequences are highly sensitive [45]
    - Identification of the location of pyomyositis can prevent seeding a sterile joint during aspiration
    - Essential tool for surgical and interventional radiology procedure planning due to its ability to show specific anatomic locations of concern
    - Contrast can increase the detection of small abscesses but is not necessary for identifying concerning edema of fluid collections
    - Postoperative MRI can identify remaining infection if there is not expected clinical improvement
  - Bone scan (Fig. 10.11)
    - Helpful in distinguishing site of pathology [46]
    - Very low specificity and sensitivity for infectious hip pathology [47]

Hip Aspiration

Aspiration of the hip should be performed as soon as possible when septic arthritis is suspected

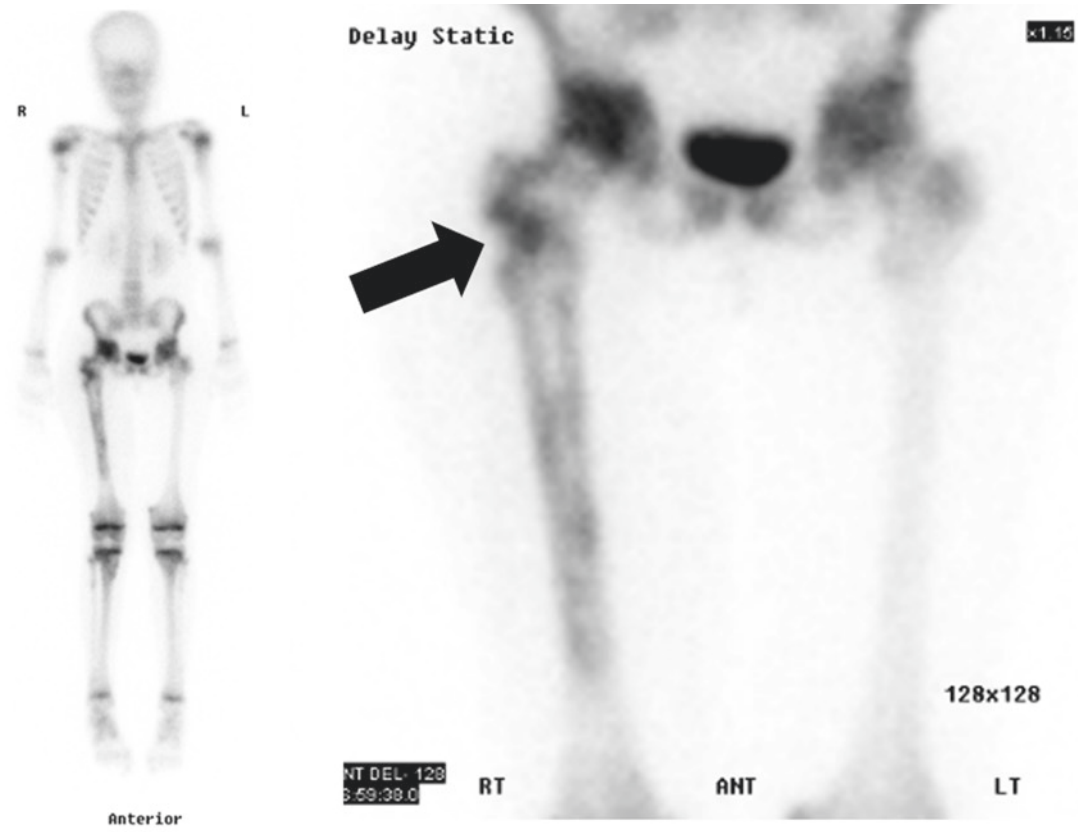

Fig. 10.11 Bone scan in hip infection. On bone scan, increased uptake can be a sign of osteomyelitis. However, it is not specific for infection but can be helpful in identifying other sites of osteomyelitis

(Fig. 10.12). Aspiration may confirm the presence of a septic joint that requires urgent surgical drainage. Additionally, despite multiple recent studies indicating that pre-treatment with antibiotics does not change the yield of local tissue aspiration, conventional treatment has been to hold antibiotics prior to aspiration [4, 5, 48–51]. Importantly, the authors recommend that antibiotics should not be held to obtain cultures, especially if the child is experiencing an exuberant acute phase response that puts them at risk for morbidity and mortality [4, 5, 49]. However, at many hospitals, it is still common practice to without antibiotics until joint cultures are obtained, thereby placing the burden of initiating treatment on the surgeon.

Using an 18- or 20-gauge spinal needle, the joint is aspirated through an anterior or medial approach under sedation with ultrasound guidance or arthrogram to assure entry into the hip. Fluid is placed in appropriate culture media and tubes for fluid analysis including Gram stain, culture, leukocyte count, and determination of the percentage of polymorphonuclear cells. A nucleated cell count of greater than 50,000 cells/mL and >75% segmented neutrophils and/or the presences of a positive gram stain/culture is generally considered to be positive for septic arthritis. In cases where the cell count is inconclusive (10,000–75,000 cells/mL), the decision to perform an arthrotomy depends on the preference of the treating physician.

"Multiple recent studies indicate that pre-treatment with antibiotics does not change the yield of local tissue aspiration".

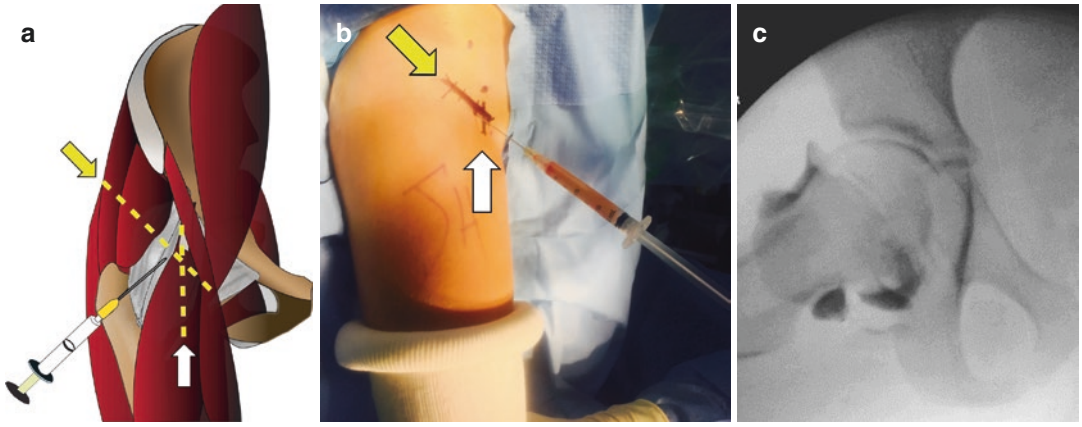

Fig. 10.12 Hip aspiration technique. (**a**) The aspiration technique centers on the hip flexion crease (yellow arrow) and the rectus tendon (white arrow). The approach is from the lateral inferior quadrant of the two lines aiming where they intersect. (**b**) The yellow and white arrows once again show the hip flexion crease and rectus tendon with the approach demonstrated with needle and syringe. (**c**) Following aspiration of synovial fluid, intraarticular aspiration should be confirmed with arthrogram

Laboratory Tests

Timely diagnosis and effective treatment dramatically changes the natural history of musculoskeletal infections about the hip. Prior to the development of antibiotics, mortality was a serious concern and even now, severe systemic disease is possible due to musculoskeletal infection. While mortality is rare with appropriate antimicrobial therapy and surgical management, patients with musculoskeletal infection have the potential for significant systemic morbidity, including venous thromboembolism (VTE), disseminated intravascular coagulation (DIC), respiratory failure, endocarditis, and multiple organ failure. Therefore, upon initial evaluation, physicians employ a multitude of tests in attempt to determine if the child has an infection, the location of the infection, and the severity of the infection. Blood and local cultures are the gold-standard laboratory tests utilized to determine if the child has an infection. Imaging and physical exam are the gold-standard methods of determining the location of an infection. The utility of these tests is limited by the time required to obtain a result. Blood and tissue cultures may require days of incubation and often return a negative result in presumptively infected patients. Access to advanced imaging, such as MRI, is not always available and often requires sedation. Therefore, over the last two decades, physicians have attempted to develop predictive tools that identify at-risk patients on the day of admission in an effort prevent these life-threatening and costly complications.

Thousands of proteins are up and down-regulated with activation of the acute phase response. By definition, proteins may be considered acute phase reactants only if they increase or decrease in quantity by greater than 25% (most of these fluctuations mediated by changes in hepatic synthesis) [52]. The magnitude of change in serum concentration and time course for resolution for different acute phase reactants varies significantly, depending on their role in activating, sustaining, or resolving the acute phase response (Fig. 10.13). With specific acute phase reactants, understanding the temporal relationship between the specific acute phase reactant and the pathogen-induced injury provides considerable diagnostic utility. For example, understanding that CRP is produced more rapidly in the liver than fibrinogen explains the increased utility in monitoring CRP as opposed to fibrinogen (or ESR—see below) in the early diagnosis of infection (Fig. 10.13 'Lab 1') as compared to later in

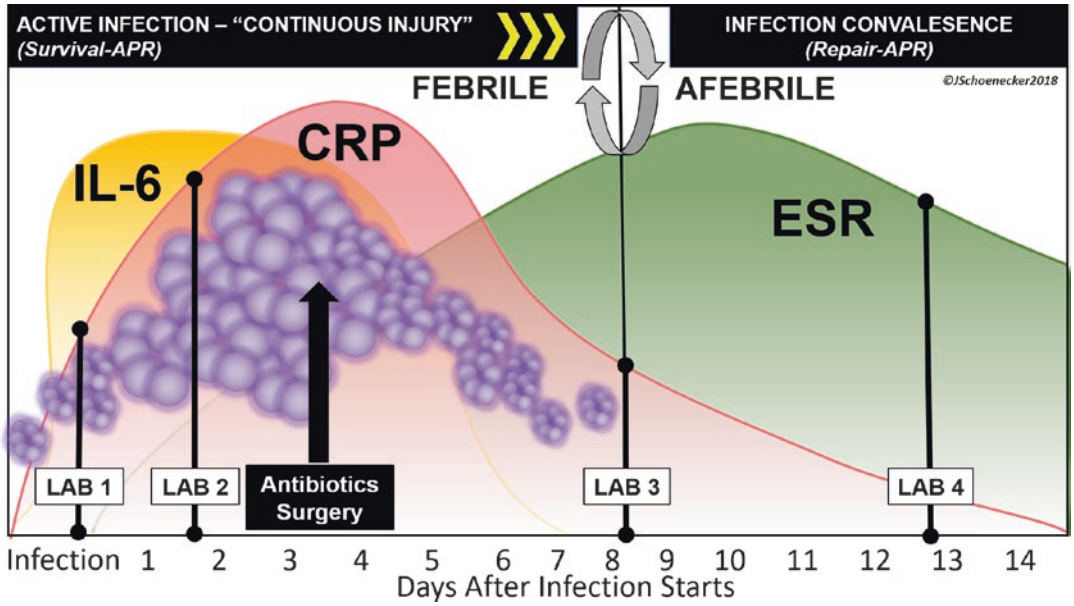

Fig. 10.13 Acute phase response markers and infection. Levels of acute phase reactants following tissue injury change dramatically and rapidly. IL-6 is the first acute phase reactant to increase, followed closely by procalcitonin (not depicted) and then CRP. In cases of severe tissue injury, CRP reaches levels more than 100 times pre-injury values. Fibrinogen (also measured as ESR) increases to a lesser degree, and takes weeks to return to its pre-injury levels. Albumin (not shown) decreases in response to the acute phase response by up to approximately 40% and often inversely correlates with CRP. The extent and duration of an acute phase response is dependent upon the severity of a tissue injury and resulting production of inflammatory cytokines such as IL-6. The magnitude of the acute phase reaction can be quantified by both the peak concentration of an acute phase reactant as well as the total amount of that reactant over time (area under the curve). Only after the infection has been controlled by antibiotics and surgery can the convalescence phase begin with tissue repair following clearance of infection

the infection (Fig. 10.13 'Lab 2'). Additionally, serial monitoring acute phase reactants may provide valuable information regarding the efficacy of antibiotics and/or debridement by observing the change over time (Fig. 10.13 compare 'Lab 2' to 'Lab 3' to 'Lab 4'). For example, with effective therapy, the CRP and other markers should consistently decline each day, with expected spikes associated with any surgical intervention [53]. If they are not declining, then further intervention is likely necessary. Because of their short half-life, it is often helpful to recheck inflammatory markers even several hours after they are first drawn and prior to performing an irrigation and debridement. Morbidity of surgery could be avoided if inflammatory markers are declining, indicating a resolving infection, even without therapeutic intervention. A review of some of the most commonly used acute phase reactants is below.

IL-6

IL-6 is the principal initiating factor in the acute phase response and is released by damaged tissue during infection (Fig. 10.13). It is stored in musculoskeletal tissue and released immediately following injury and therefore provides the earliest measurable response to tissue damage [54]. IL-6 has been studied as a potential marker for assessing prognosis and guiding treatment in the setting of trauma, sepsis, and heart disease [54–57]. However, there is limited literature describing its use in the context of musculoskeletal infection, likely because measurement of IL-6 has associated challenges, such as limited availability for testing in the clinical setting, short half-life in plasma, and absence of standardization. Currently, its measurement for gauging musculoskeletal infection severity is limited mainly to research settings.

CRP

C-reactive protein is produced by the liver in response to IL-6 and other cytokines (Fig. 10.13). The origin of the name derives from C polysaccharide of Streptococcus pneumonia [58]. At a molecular level, CRP has several defined roles. It has the capability to bind dying cells and/or bacterial pathogens and activate the complement system [59]. In addition, CRP is able to activate monocytes and induce the release of inflammatory cytokines [60, 61]. In response to acute episodes of tissue injury, there are short but substantial increases in the levels of serum C-reactive protein. In fact, it is one of the most drastically induced acute phase reactants with levels increasing more than 100-fold in the immediate post-injury period [62]. In addition, as one might expect, the magnitude of the increase in CRP correlates with the scale of tissue injury. In contrast to ESR and fibrinogen, which have long half-lives, CRP has a half-life of only 17 h and levels increase within 4–6 h of injury [63]. Therefore, it can be used to track real-time responses to therapy and guide care for musculoskeletal infection (Fig. 10.6) [64].

Mild baseline elevations in CRP are seen in the context of chronic diseases, such as coronary artery disease and diabetes. On the other hand, markedly elevated CRP levels are more indicative of an acute inflammatory process, such as bacterial infection [65]. Because of the correlation between CRP and tissue injury, CRP has been included in a number of prognostic and diagnostic models that help guide treatment in infection [9]. One of these is the scoring system for assessment of severity of illness in the context of pediatric acute hematogenous osteomyelitis [8]. In this model, osteomyelitis was stratified into mild, moderate, and severe categories based on objective clinical parameters. Not surprisingly, CRP values at admission, 48 h, and 96 h all significantly correlated with disease severity and outcomes, such as total length of stay. Other models have similarly utilized CRP as a marker of disease severity. For example, Martin et al. also developed a prediction model that showed that children with a higher CRP at admission were more likely to develop complicated osteomyelitis [66]. CRP is also included in the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score as a CRP of greater than 150 mg/L in the system suggests an increased likelihood of necrotizing infection [67]. Overall, the marked elevation of CRP in the setting of acute inflammation and its short half-life make it an effective marker for gauging infection severity and monitoring response in clinical settings. Notably, the units for CRP measurement may vary by institution by a factor of 10, with some hospital reporting CRP in units of mg/dl, while others report in units of mg/L.

ESR and Fibrinogen

The ESR is a simple, indirect measure for the acute phase response (Fig. 10.13). The ESR measures the rate of descent of anticoagulated red blood cells in a vertical column in 1 h. This measurement is influenced by numerous factors, the most important being the concentration of the acute phase reactant fibrinogen. While ESR advanced medical science when introduced in the 1920s, it is often misleading because it is greatly influenced by immunoglobulins, plasma constituents, and changes to erythrocyte morphology and number. Thus, ESR is a less sensitive marker for the APR than fibrinogen [22, 53]. Nevertheless, out of convention, most clinicians continue to monitor and report ESR in studies.

Currently, an elevated ESR is a key diagnostic criterion for several non-infectious diseases including polymyalgia rheumatic and temporal arteritis and is often used as an adjunct ‘severity index’ in the context of infection. However, there are also several non-inflammatory etiologies of elevated ESR including anemia, pregnancy, obesity, and old age, making it a less specific marker for infection or inflammation [68, 69]. Fibrinogen is a relatively late rising acute phase reactant and has a long half-life. As such, ESR typically increases 24–48 h after initiation of the acute phase response and decreases slowly with resolution of inflammation.

In the context of musculoskeletal infection, ESR has been used as a predictive marker for severity of several different diseases processes. One study

demonstrated an increased likelihood of diabetic foot osteomyelitis in the setting of appropriate symptoms and an ESR greater than 70 mm/h [70]. In addition, ESR levels remain elevated for a prolonged period post-infection (up to 3 months), which has led authors to suggest using ESR for monitoring long-term recovery [71]. In the context of pediatric musculoskeletal infections, ESR greater than 20 mm/h had 94% sensitivity for detecting musculoskeletal infection [72]. Based on these studies, it is evident that an elevated ESR has been utilized effectively as a marker of infection severity, with a relatively high sensitivity as a potential screening index for musculoskeletal infection.

Procalcitonin

Procalcitonin, a peptide precursor of calcitonin, is another acute phase reactant that has been studied for use in the diagnosis and treatment of musculoskeletal infection. While calcitonin is typically secreted by the parafollicular cells of the thyroid in response to hypercalcemia, the biological function of procalcitonin is largely unknown. Procalcitonin is synthesized in the neuroendocrine cells of the lungs and intestine in response to cytokines including IL-1, IL-6, and TNF-alpha. Serum concentrations are normally undetectable, but have been shown to increase a thousand-fold in the setting of systemic bacterial infections [73]. 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 h of treatment initiation [74].

Currently, there are few studies that examine the use of procalcitonin in the context of musculoskeletal infection. One meta-analysis based on these studies 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 [75]. Interestingly, current studies suggest that procalcitonin may have several advantages over CRP as a marker of musculoskeletal infection severity. It increases earlier than CRP in response to IL-6, reaching half of its maximum value in 8 h compared to 20 h for CRP [76]. It also has a shorter half-life, which means that its levels begin to fall earlier than CRP with the resolution of inflammation [77, 78]. Additionally, procalcitonin does not increase significantly in the context of viral or non-infectious pathology, potentially making it a more specific test than CRP in the setting of bacterial infection [79–81]. In fact, Simon et al. found that procalcitonin is more accurate than CRP in differentiating infection from non-infection and bacterial infection from viral infection [82]. Overall, procalcitonin appears to be a promising inflammatory marker, but further research is necessary to characterize its response in the setting of musculoskeletal infection.

Additional Acute Phase Reactants

There are thousands of additional proteins modulated by the acute phase response. In addition to IL-6, several other inflammatory cytokines also act as initiators of the acute phase response, including transforming growth factor beta, interferon gamma, and tumor necrosis factor alpha [83]. These cytokines are produced predominantly by macrophages at sites of injury and inflammation, and they have a similar role in stimulating the coagulant, inflammatory, and regenerative arms of the acute phase response [53].

Given the wide range of proteins influenced by the acute phase response, the hepatic response to tissue injury has far reaching physiologic effects. Studies have demonstrated that inflammatory cytokines significantly impact the hypothalamic-pituitary-adrenal axis, including leading to secretion of corticotropin-releasing hormone and increased cortisol production. This interaction with the body's central hormonal regulation contributes to many of the systemic symptoms that are typically associated with inflammatory conditions such as infection [84].

Negatively Regulated Acute Phase Reactants

Although most proteins affected by the acute phase response are upregulated to propagate the acute phase response, there are many proteins whose

production is inhibited in response to tissue injury. These are termed negative acute phase reactants and include proteins such as albumin, transferrin, and transthyretin [53]. Decreased production of these proteins may serve to divert resources toward synthesis of proteins directly involved in the acute phase response. In addition, the decrease in level of certain proteins may also have a pro-inflammatory effect. For example, transthyretin has been shown to inhibit IL-1 production by monocytes [85]. Therefore, a decrease in production of transthyretin increases the inflammatory effects of IL-1, leading to fever and immune cell adhesion factor expression. Given their inverse relationship to the acute phase response, these proteins have the potential to be monitored as markers of the intensity of the acute phase response in the opposite manner of markers such as CRP and ESR. In the case of these negative acute phase reactants, marked decreases in plasma expression would be indicative of a more robust acute phase response.

Nonoperative Management

Antibiotics

Antibiotics are the first line therapy for infection around the hip when septic arthritis, osteomyelitis or pyomyositis is present without evidence of abscess formation (Table 10.1). Appropriate timing of administration requires balancing the priorities of identifying the causative organism and avoiding delay of treatment. In multiple studies, antibiotics do not reduce culture yields from the site of infection [4, 5, 51]. Because musculoskeletal infections can progress to sepsis quickly and complications, while rare, can be devastating, treatment should not be delayed for extended periods. Initial antibiotic choice is dependent on the local microbiogram and based on patient factors. For example, neonates are at increased risk of exposure to hospital acquire pathogens, including MRSA, Candida, Enterobacteriaceae or group B Streptococcus [86–88]. Therefore, they should be treated with ampicillin, cefotaxime vs gentamycin, acyclovir and vancomycin in regions with high prevalence of MRSA [87, 89]. When the infection appears less virulent, K kingae should be suspected which is effectively treated by ceftriaxone. Antibiotic treatment of pyomyositis and septic arthritis mirrors that of osteomyelitis with antibiotic choice based on local and patient factors. Treatment duration is dependent on response and the type of tissue affected, but this is still controversial. Many pediatricians recommend 2–4 weeks of IV antibiotics for osteomyelitis, followed by oral antibiotics for a total

Table 10.1 Antibiotic treatment of musculoskeletal hip infection

Age	Site	Pathogens of concern	Empiric antibiotic	Duration
<1 month		Group B Strep Enterobacteriaceae S. aureus	Augmentin Gentamycin	3–4 weeks for soft tissue infection, 4–6 weeks for osteomyelitis
>1 months and <4 years	Bone	S. aureus S. Pyogenes K. Kingae Enterobacteriaceae	Clindamycin or Vancomycin + Rifampin + Ceftriaxone	IV antibiotics followed by oral antibiotics totaling 4–6 weeks
	Soft tissue	S. aureus S. pyogenes K. Kingae Enterobacteriaceae	Clindamycin or Vancomycin + Ceftriaxone[a]	3–4 weeks high dose oral antibiotics
>4 years	Bone	S. aureus S. pyogenes	Clindamycin or Vancomycin + Rifampin	IV antibiotics followed by oral antibiotics totaling 4–6 weeks
	Soft tissue	S. aureus S. pyogenes	Clindamycin or Vancomycin[a]	3–4 weeks high dose oral antibiotics

Whenever multiple tissue types are affected, defer to the longer treatment timeline
[a]Add doxycycline or amoxicillin × 30 days when concerned about Lyme arthritis

6- to 8-week course. However, some studies are suggesting that several days of IV antibiotics with a good response (decrease in CRP by 50%) followed by 2–4 weeks of oral antibiotics may be adequate [89]. Treatment for septic arthritis and pyomyositis is usually shorter and can even be limited to 2–3 weeks of large dose oral antibiotics [90]. Treatment should defer to the longest course needed for treatment based on the tissue type affected i.e. children with septic arthritis and osteomyelitis should be prescribed an antibiotic course long enough to treat osteomyelitis.

Essential Non-operative Management

1. Early antibiotics is the mainstay of treatment
   (a) Does not reduce tissue culture yields in musculoskeletal infection
   (b) Proven effective in reducing mortality in sepsis
   (c) Should be tailored to hospital/regional biogram
      - S. aureus is the most common pathogen and MRSA should be covered as well in most areas
2. Monitor the acute phase response with inflammatory markers with concern if increasing over the first day
3. Trial of anti-inflammatory (e.g. ketorolac) can be helpful in lowering suspicion if there is significant improvement in symptoms
4. Systemic steroids may shorten length of stay and negative sequelae of infection [91, 92]

Special Considerations: Dysregulation of the Acute Phase Response

The acute phase response is crucial for clearing infection and healing damaged tissue through regulation of inflammatory, coagulant, and immune processes. However, dysregulation of the acute phase response has the potential to lead to severe complications related to these same processes, such as hypotension, septic shock, and coagulopathy (Fig. 10.7). These complications are much more likely to occur in the context of severe, disseminated infections, due to intense up-regulation of the acute phase response.

Septic and Toxin-Mediated Shock

One of the most severe complications of infection is shock, which carries a mortality of up to 20% in children [93]. In musculoskeletal infection, this may occur due to septic shock or toxic shock syndrome. Toxic shock syndrome is most often caused by S. aureus and S. pyogenes production of super antigens, such as toxic shock syndrome toxin (TSST) and streptococcal superantigens, respectively. These toxins produced by S. aureus and S. pyogenes are structurally related and act by binding MHC II and T cell receptors, leading to the widespread activation of antigen-presenting cells and T cells [94, 95]. This activation leads to the release of high systemic levels of cytokines such as TNF-alpha, TNF-beta, IL-1, and IL-2, thereby generating an over-exuberant inflammatory response that is characterized by fever, hypotension, rash, and other systemic symptoms [96, 97]. Of these cytokines, TNF-alpha has been shown to be the most significant mediator of the shock response and its inhibition has been shown to improve mean arterial pressure and survival in animal studies [98].

Septic shock results from a hyper-inflammatory immune response due to overwhelming, systemic bacterial infection. Higher levels of acute phase reactants are indicative of worse prognosis and indicate the need for aggressive intervention. Interestingly, following intense activation of the acute phase response secondary to infection, many patients also experience a state of immunoparalysis, due to a strong compensatory anti-inflammatory response [99]. Studies have demonstrated that people who die of sepsis and multiple organ failure sometimes have biochemical immunohistochemical evidence of immunosuppression with CD4, CD8, and HLA-DR depletion and decreased levels of IL6,

IL10, and interferon gamma [100]. This immunosuppression associated with septic shock is due to increased apoptosis of immune system cells, T cell exhaustion, monocyte deactivation, and the regulatory effect of CNS immune system [99]. It is crucial to remember that acute phase response reactants and mediators are finite and may be depleted, leading to complications in the late stages of severe infections.

Coagulopathy

Severe cases of musculoskeletal infection have the potential to dysregulate the acute phase response, leading to systemic coagulopathy and disseminated intravascular coagulation (DIC) [25]. Thrombosis is a common complication of musculoskeletal infection and epidemiologic studies have detected venous thromboembolism in up to 10% pediatric patients with hematogenous osteomyelitis [101–104]. Additional studies have shown that dissemination of musculoskeletal infection predisposes patients to developing severe coagulopathy [25, 105].

Disseminated intravascular coagulation has the potential to cause widespread thrombosis along with paradoxical bleeding, leading to mortality rates around 50% [106, 107]. The combined hyper and hypocoagulable state of DIC poses a dilemma for effective treatment. Therefore, in the setting of severe musculoskeletal infections, regular assessment of markers such as PT, PTT, fibrinogen, and D-dimer may be warranted to detect early coagulopathic changes and allow for timely administration of clotting factors and platelets [25].

Disseminated intravascular coagulation is characterized by systemic activation of the coagulation system with deposition of fibrin and platelets throughout the vasculature [108]. The activation of the coagulation cascade is dependent on the activation of the tissue factor/factor VIIa pathway and the contact system. In addition to uncontrolled coagulation, anticoagulant pathways also become dysregulated in DIC, most notably the protein C, antithrombin, and tissue factor pathway inhibitor cascades [109]. Protein C levels are decreased by impaired synthesis, consumption, and degradation. In addition, its activation is decreased by proinflammatory cytokines [110]. Furthermore, sepsis leads to downregulation of endothelial protein C receptors and resistance to activated protein C via increased factor VIII levels [111, 112]. Several clinical trials have attempted to improve sepsis outcomes by administering activated protein C, but these studies have failed to demonstrate benefit and identified an increased bleeding risk. Antithrombin, another anticoagulant, inhibits both thrombin and factor Xa to prevent hypercoagulability. However, during severe inflammation, antithrombin levels are decreased by impaired synthesis, neutrophil elastase degradation, and consumption [113]. Similar to protein C studies, clinical trials investigating repletion of tissue factor pathway inhibitors, such as antithrombin, have demonstrated increased bleeding risks without improvement in mortality [114].

Monitoring Coagulation in the Setting of Coagulopathy

The combined hyper- and hypocoagulable state of DIC due to widespread dysregulation of coagulation cascades poses a dilemma for both diagnosis and treatment [108]. Therefore, in the setting of severe infections, laboratory tests such as PT, PTT, fibrinogen, and D-dimer may be warranted to detect early coagulopathic changes and allow for timely administration of clotting factors and platelets.

Critically ill patients with DIC often have platelet counts in the range of 50,000–100,000, if not lower [115]. Therefore, close monitoring of platelet count in the beginning stages of severe infection may allow for early transfusion and prevention of significant bleeding. PT/INR is commonly used as a marker of patient's coagulation status. While this test was originally developed to measure the effects of warfarin on the clotting cascade, the accuracy, availability, and familiarity of the test has made it a widely used marker of coagulopathy [116]. Direct measurement of coagulation factors to assess for coagulopathy

is not currently recommended as the tests often have delayed turnaround times and most assays require factors to be less than 50% of their normal levels to be considered significant.

Fibrinogen is one of the most commonly measured coagulation factors but is a nuanced marker in diagnosing DIC. While it is an acute phase reactant that is highly upregulated in the setting of infection, it is also consumed rapidly in the setting of DIC. Therefore, a single measurement of fibrinogen in the setting of severe sepsis may be difficult to interpret accurately. However, a low fibrinogen level is suggestive of serious coagulopathy, with consumption outpacing the accelerated production caused by the acute phase response. Fibrin degradation products such as D-Dimer may be used as a proxy for the rate of fibrinogen consumption and clot formation. However, this test is dependent on the rate of fibrinolysis, which can also be variable in the setting of acute disease.

One test that offers a comprehensive picture of the coagulation and fibrinolytic systems is thromboelastography (TEG), which measures the speed and strength of clot formation from a sample of blood. It provides measurements of clot kinetics, strength, and lysis, allowing for a more comprehensive measurement of coagulation and fibrinolysis. Unfortunately, this test is not commonly used in the context of coagulopathy and DIC, but is gaining popularity in the setting of trauma [117]. A recent prospective observational study demonstrated that hypocoagulability identified with TEG correlated with increased bleeding and mortality in the context of severe sepsis [118]. Further studies are required to define the potential utility of this test in the context of DIC and musculoskeletal infection in pediatric patients.

Operative Management

Septic arthritis should be treated with irrigation and debridement of the infected joint on an urgent basis. Good outcomes are usually achieved if this is done within 5 days of the clinical onset of infection. Most practitioners feel comfortable waiting until the next morning to take a child to the operating room to treat their infection, rather than operating in the middle of the night. There are several options for surgical treatment of septic arthritis. For septic arthritis, the most commonly used approach is the anterior, or Smith Petersen, approach to the hip (Fig. 10.14). This approach utilizes the interval between the Sartorius and tensor fascia latae (TFL), then the interval between the rectus femoris and the gluteus medius/minimus. The Watson Jones (anterolateral) approach can also be used to reach the hip but requires partial release of the abductors and reflection of the head of the rectus femoris, so it is less commonly used. Lastly, the Southern Moore posterior approach can also be used to reach the hip capsule, but again requires more soft tissue dissection and is not commonly used. However, if there are abscesses that require debridement, choice of approach should consider accessing not only the joint, but the affected musculature as well. For example, a medial approach can be used to drain and debride pyomyositis of the obturator musculature without the extensive dissection or danger to the femoral vessels and nerve of an ilioinguinal of Pfannenstiel approach [119]. In addition to these open approaches to septic arthritis, the hip can be cleaned arthroscopically as well with excellent results, including an approach through a medial portal [120–122]. Two drawbacks of arthroscopy, however, are that they do not permit debridement or drainage of adjacent pyomyositis and the small size of some children makes the approach technically difficult. In most cases a drain is left in place and removed 2–3 days after surgery once inflammatory markers have decreased and the patient has improved clinically. For children who do not demonstrate improvement within the first 72–96 h, repeat imaging may reveal other sources of infection around the hip joint and a return to the operating room for a second irrigation and debridement may be necessary.

In the early stage of pyomyositis when there is only inflammation of the muscle and no abscess, the first line of treatment is medical, with empiric antibiotics. Once this has been started, the patient is monitored for improvement in clinical exam

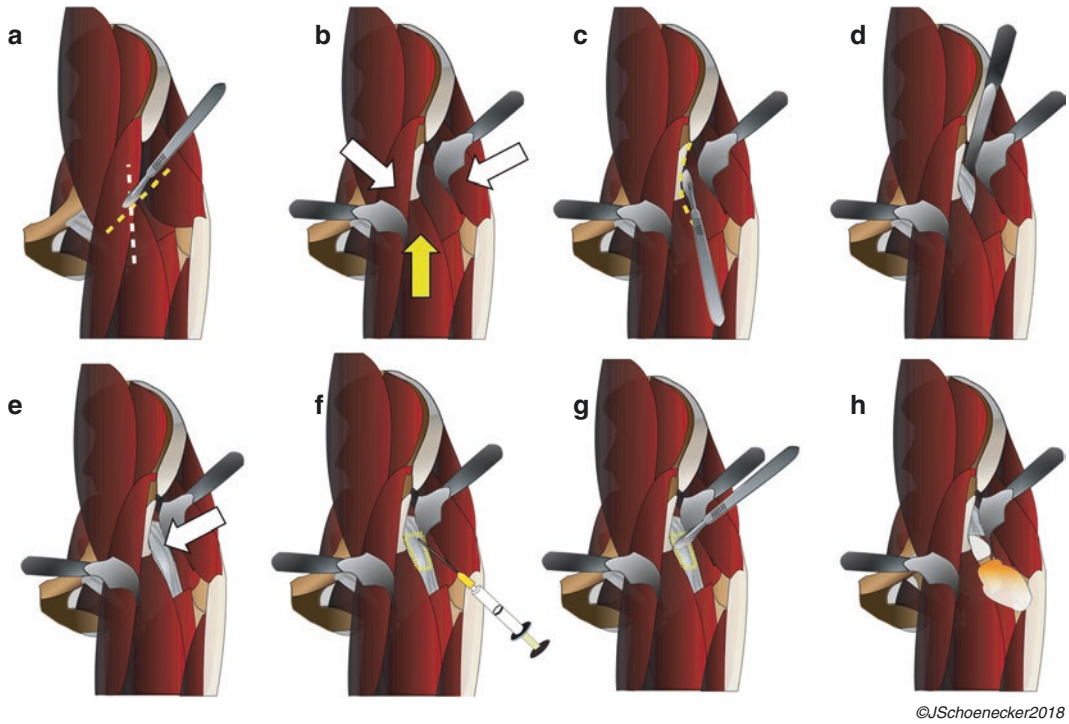

Fig. 10.14 Anterior debridement of the hip. (**a**) Identify the hip crease by flexing hip, externally rotating the leg to accentuate the gap between Sartorius and tensor fascia lata (TFL) and help identify the interval before incision from the ASIA distally through skin and subcutaneous tissue. Debridement centers on the intersection of the (**b**) white arrows showing the sartorius (retracted medially to protect the lateral femoral cutaneous nerve) and TFL. Use blunt dissection, identify the conjoint tendon entering the reflected rectus tendon (yellow arrow) (**c**). Make an incision along the gluteus minimus that joins the conjoint tendon being careful to avoid the circumflex vessels at the distal portion of the interval. (**d**) Use a Cobb to peel gluteus minimus off the hip capsule, (**e**) Exposing the hip capsule. (**f**) With the capsule exposed aspirate synovial fluid for culture. (**g**) Take a 1 cm cube of hip capsule for culture and to (**h**). Release the contents of the hip capsule, irrigating copiously and leaving a drain after debridement is complete

and inflammatory markers. If no improvement occurs after 2–3 days, then repeat MRI can be helpful to evaluate for progression of disease. When advanced imaging shows frank abscess formation, the first line of treatment is evacuation of the abscess either by surgical debridement in the operating room, or by placement of a drain by interventional radiology. As in other types of infection, when MRI demonstrates effusion in a surrounding joint, this should not be ignored, and the joint should be aspirated and evaluated for the presence of a bacterial septic arthritis.

In cases of osteomyelitis where imaging findings that show abscess formation (intra-osseous, sub-periosteal or extra-periosteal), surgical debridement is indicated. Intraosseous debridement is done by making a cortical window in the region of the affected bone, with care taken not to injure the growth plate. Any adjacent areas of infection, such as sub or extra-periosteal abscesses, should be drained at the same time. If a hip effusion is present as well, the joint should be aspirated and evaluated for the presence of bacterial septic arthritis.

Post-operative weight bearing depends on the extent and location of the debridement to avoid pathologic fracture. Children are monitored after initiation of treatment for improvement in their inflammatory markers as well as their clinical exam. Children who fail to improve should be carefully evaluated to determine if repeat MRI is warranted. Repeat imaging in the

early postoperative setting is advised only if the treating provider feels that there is a previously unaddressed focus of infection. Otherwise, clinical and laboratory examinations should be used to guide the decision for repeat surgical intervention of know, or previously addressed foci of infection.

One current controversy in the treatment of hip infections is the need for drilling proximal femur osteomyelitis. Due to concern for avascular necrosis, traditional teaching has been that drilling of proximal femoral osteomyelitis is necessary to relieve pressure and reduce bacterial burden [123]. However, animal studies have suggested that drilling of osteomyelitis and curettage may only cause damage to the bone, destroying intramedullary blood supply and serving to more widely inoculate the area with bacteria [124]. Additionally, drilling of the femoral neck and proximal femur further weakens the bone which is already at risk for fracture due to infection. Furthermore, improvement in antibiotics likely obviates the need for bony debridement, and antibiotic administration does not reduce culture yields even if debridement is felt to be necessary in the future [4, 5]. For these reasons, the authors no longer drill all proximal femoral osteomyelitis.

Because of these complications, effective diagnosis and treatment is necessary. Therefore, understanding the anatomic location of the infection is also necessary. Debridement of the hip joint itself is often unnecessary or insufficient. Therefore, advanced imaging can be helpful in establishing a proper diagnosis. In fact in one epidemiologic study, pericapuslar pyomyositis was twice as common as septic arthritis [18]. While there is likely variation between regions, infection is rarely isolated to one part of the hip and frequently involves other joints and the bloodstream. Therefore, while repeat aspirations of the hip for treatment of septic arthritis may be effective in some cases, others that include abscesses in the surrounding musculature will require either radiographically guided drain placement or surgical debridement [125]. In cases of isolated septic arthritis, repeat aspiration may be an effective treatment, but the patient must be closely monitored for clinical improvement. Surgical treatment is also an excellent option; however, it carries the morbidity of an incision and dissection. Additionally, the evidence for when surgery is needed is poor.

Essential Operative Techniques

- Early debridement of septic arthritis or pyomyositis may be necessary to prevent complications
- The timeline of proper surgical treatment is still poorly understood
- Numerous approaches exist to debridement and lavage of the hip
- Drilling of proximal femoral osteomyelitis may or may not help prevent septic arthritis and AVN

Case Example

Two six-year-old boys presented with similar findings. Each demonstrated an antalgic exam with minimal tolerance of hip movement and preferred holding their hips in a flexed abducted and externally rotated position, even when sedated (Fig. 10.15). Both children were febrile and had elevated CRPs. Neither had significant findings on X-ray. Child A demonstrated a large effusion by US (Fig. 10.8), whereas Child B had only a mild effusion (Fig. 10.17). MRI revealed an isolated effusion in Child A and significant pyomyositis in Child B (Fig. 10.17).

Child A was treated with anterior debridement of the hip (Fig. 10.14) and his course initially improved, but then rapidly worsened as indicated by up-trending CRP and worsening clinical exam (Fig. 10.16). Cultures from the operative debridement indicated a Staphylococcus aureus resistant to the initial antibiotics. Antibiotics were changed appropriately, and the child recovered without complication or need for further debridement.

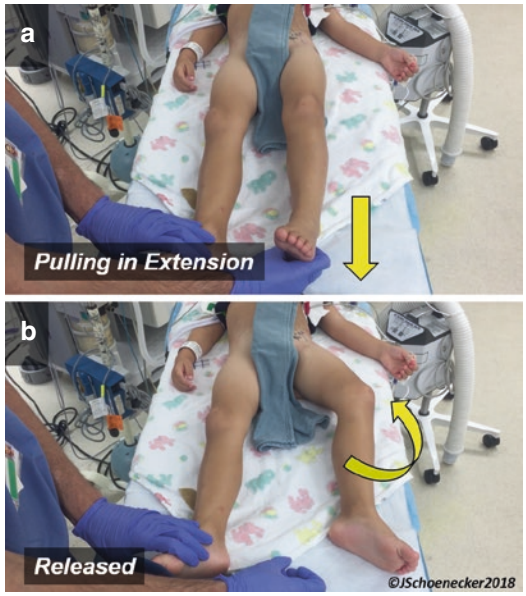

Fig. 10.15 Physical examination under anesthesia. (**a**) A child with septic arthritis of the left hip is placed under general anesthesia and the leg is pulled into extension. (**b**) However, even when asleep, the thigh is immediately pulled into a flexed, externally rotated and abducted position

MRI findings in Child B revealed significant abscess in the obturator internus that was obstructing the urethra (Fig. 10.17). Therefore, the child was taken to the operating room and the abscess was debrided and a drain placed through the Vanderbilt medial approach (Fig. 10.18) [119]. Despite the hip effusion (Fig. 10.17) detected both by US and MRI, the intra-operative aspiration was benign and therefore the hip was not opened as to not allow inoculation by the surrounding pyomyositis. The patient had immediate relief and return of continence. Follow up MRI revealed return of normal anatomy without signs of permanent disability.

Classic Papers

Hobo T. Zur pathogenese der akuten haematogenen osteomyelitis, mit breucksichtigungder vitalfarbungs leher. Acta Sch Med Kioto. 1921 [13]. The initial work detailing the anatomic characteristics of developing bone making it suceptible to infection as detailed in Fig. 10. 3.

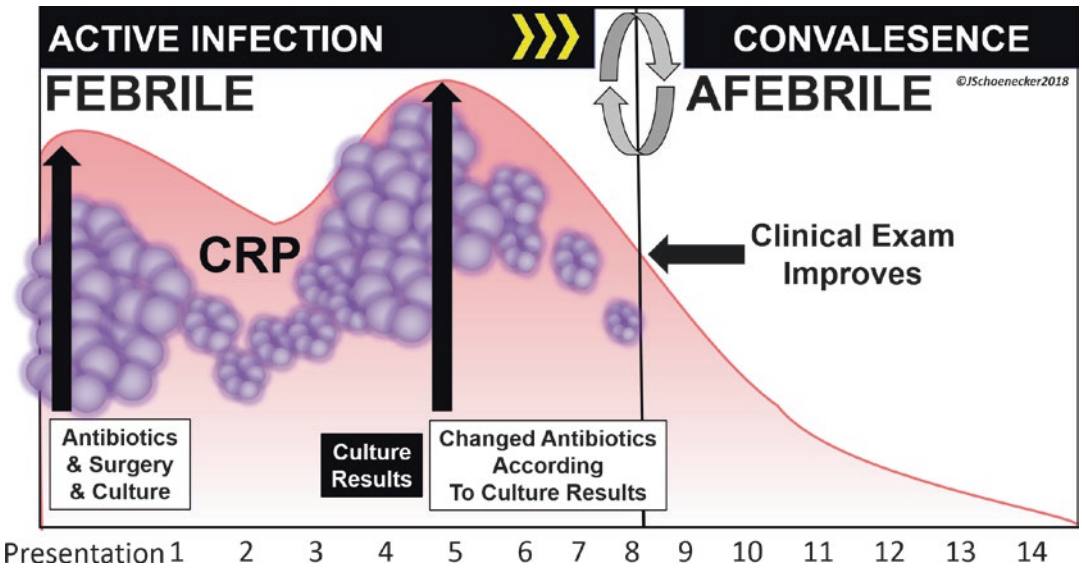

Fig. 10.16 CRP trend in pediatric hip infection. Early treatment is essential in treating hip infection, with antibiotics and surgery leading to a decrease in CRP over the first 2 days. However, it began increasing again over day 3 and 4. At that time culture results showed inadequate antibiotic therapy. The antibiotics were adjusted on day 5 and the CRP once again began trending in the correct direction and the clinical exam improved. The body had entered the convalescent stage as tissue repair began. This case highlights the importance of culture directed therapy. It is essential to obtain culture material during debridement to guide antibiotic therapy

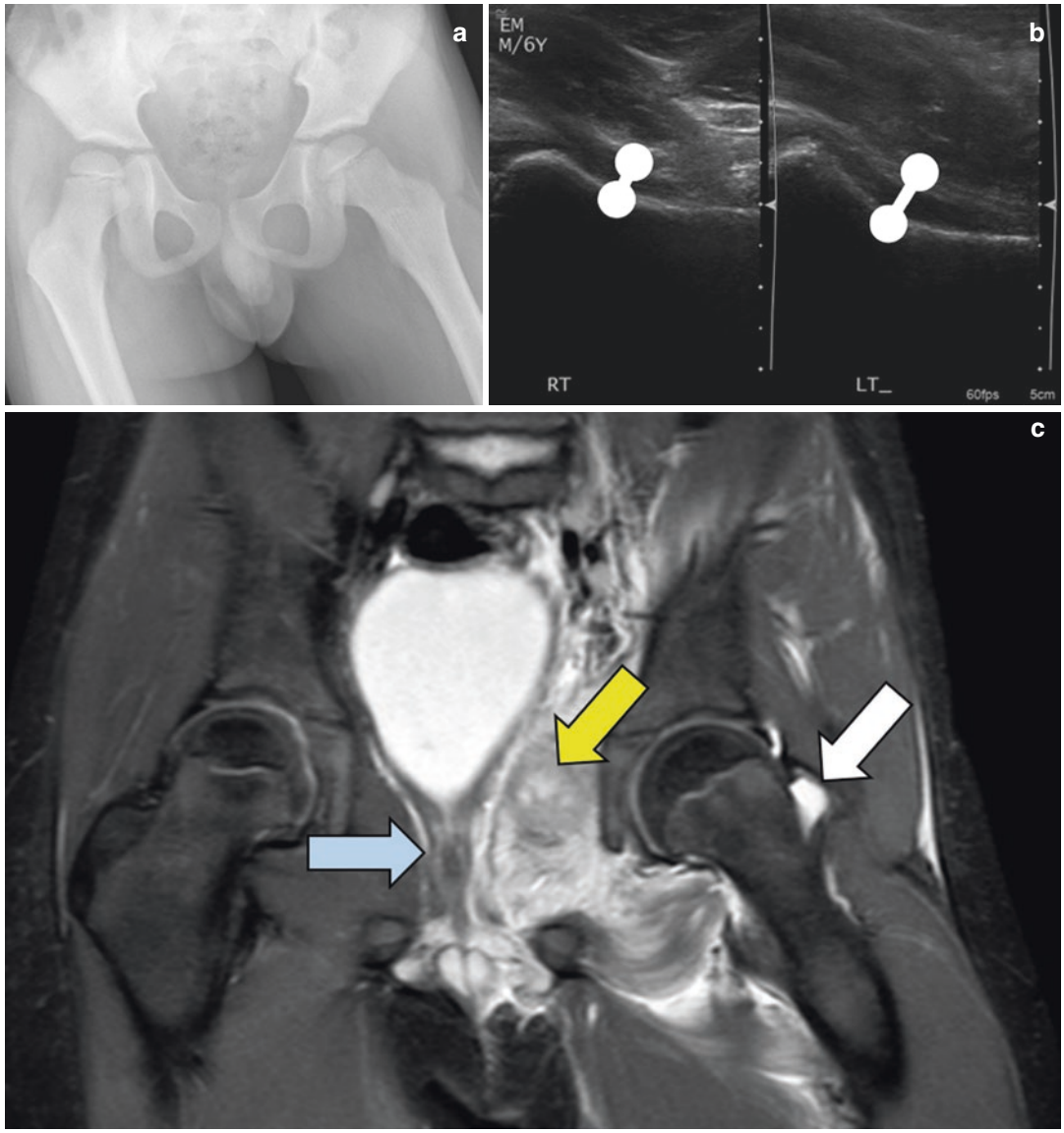

Fig. 10.17 Comprehensive imaging of hip infection. MRI is the most useful method for imaging of the infected hip. (**a**) Radiographs show the hip being held in a flexed, externally rotated, and abducted position. (**b**) Ultrasound shows a small hip effusion. (**c**) MRI re-demonstrates the hip effusion but also reveals extensive pyomyositis of the hip musculature extending to involvement of the urethra

Trueta J. The normal vascular anatomy of the human femoral head during growth. J Bone Joint Surg Br. 1957 [16]. The most comprehensive work detailing the vascular anatomy, and potential consequences of its loss, in the human proximal femur.

Ogden JA, Lister G. The pathology of neonatal osteomyelitis. Pediatrics. 1975;55 (4):474–478 [15]. A summation of original research, and other's work, regarding the characteristics of bone that make it suceptible to infection as well as modern approaches and therapy of the time.

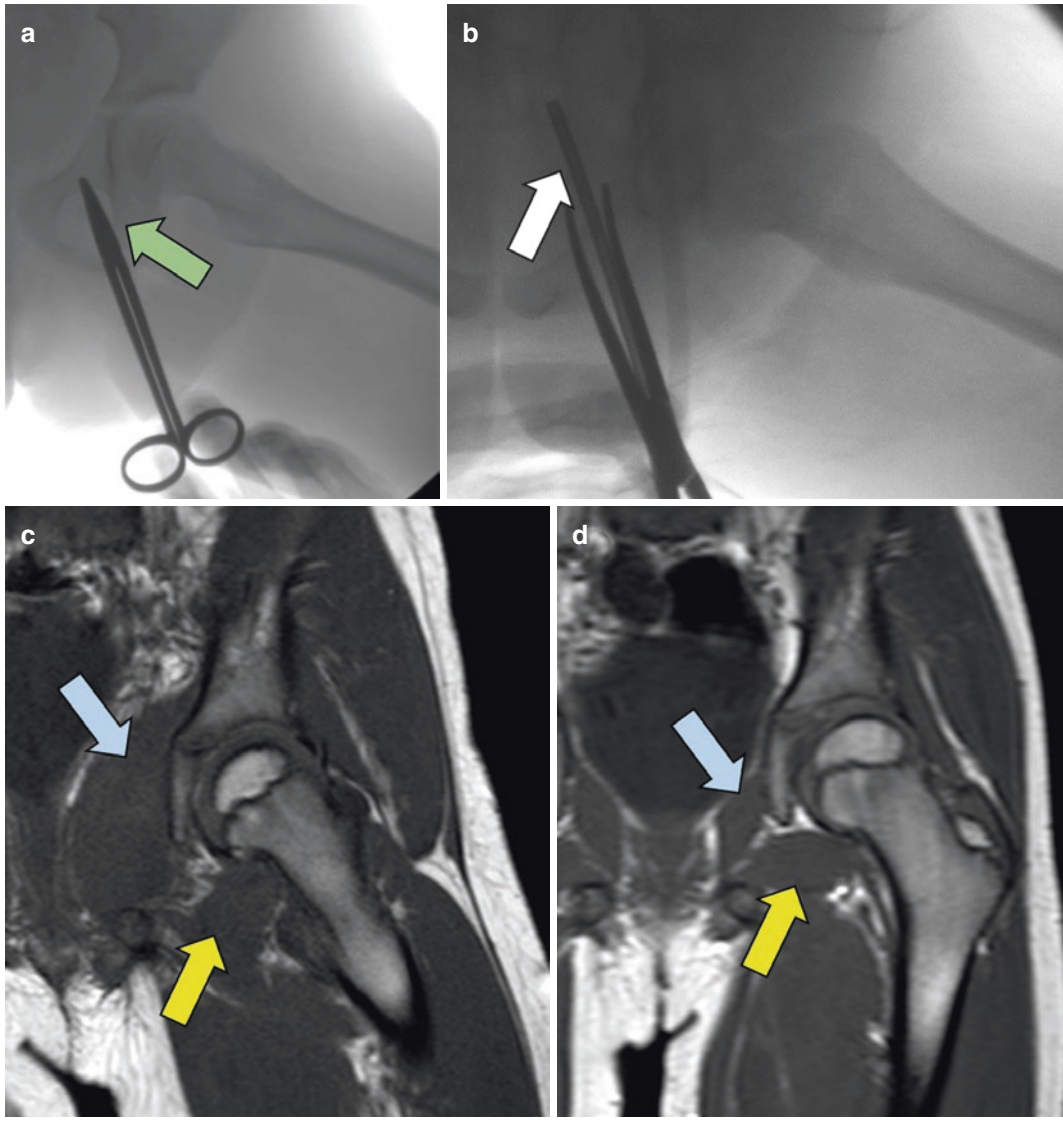

Fig. 10.18 Vanderbilt medial approach to the pelvic musculature. Drainage of the obturator musculature that was infected in Fig. 10.17 can be accomplished via a medial approach as in for a Tonnis osteotomy. The obturator externus can be debrided through the adductor brevis and the obturator internus through the obturator foramen. MRI is essential in identifying the location of the pyomyositis. (**a**) Scissors are shown entering the obturator foramen to drain the obturator internus. (**b**) Placement of a drain follows operative debridement. (**c**) Initial MRI shows a greatly enlarged obturator internus secondary to infection and inflammation. (**d**) MRI several days later shows dramatically reduced size of the obturator internus after successful debridement and antibiotic therapy

Key Evidence

Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence based clinical prediction algorithm. **Kocher et al.** [39]**.** This is the original paper establishing the now ubiquitous Kocher criteria and established a predictive model for identifying infected patients. Further studies have helped establish that this model is useful for raising sus-

picion for hip infections but did not perform as well in subsequent validation studies.

Deep venous thrombosis associated with osteomyelitis in children. Hollmig et al. [103]**.**

Children with osteomyelitis are at increased risk of developing DVT especially when admitted with a markedly elevated CRP. This paper helped to establish the importance of monitoring the inflammatory response and treating its sequelae in pediatric musculoskeletal infection.

Pediatric musculoskeletal infection: hijacking the acute-phase response. An et al. [2] Review of the role of the acute phase response in fighting infection and how pathogens have evolved to both evade and take advantage of this response. It helps to explain why musculoskeletal infection leads to its observed clinical sequelae.

Take Home Message

The case example presented above (see section "Operative Management") highlights the need for modern management of pediatric hip infection. Once the most common cause of death in the pediatric population, musculoskeletal infection is now manageable without significant death or disability if physicians can provide rapid diagnosis and treatment. Diagnosis is best made through a combination of physical exam, measuring the acute phase response, imaging and hip aspiration. The cases presented above highlight the need for MRI, given that both children presented with equivalent physical exams, measures of the acute phase response and hip effusions. Without MRI, Child B would historically have undergone the similar treatment as Child A thereby exposing the hip joint to infection, instead of protecting it. Even with the correct and efficient surgery, the mainstay of treatment is antibiotics. Thus, cultures are essential to direct therapy, as demonstrated by Child A, whose worsening course was effectively treated by using information regarding bacterial susceptibility to antibiotics, not further surgery. Monitoring the acute phase response is the most objective way to determine the efficacy of antibiotics and need for change in therapy, or repeat debridements, in the setting of a worsening acute phase response.

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