Management of Osteomyelitis in Sickle Cell Disease: Review Article

Abstract

Sickle cell disease (SCD) is an autosomal recessive disorder that is characterized by abnormal “sickle-shaped” erythrocytes. Because of their shape, these erythrocytes are more likely to become trapped in small slow-flowing vessels, leading to vaso-occlusion. Because this commonly happens in the bones, patients with SCD are at an increased risk for orthopaedic manifestations such as osteomyelitis, septic joint, or osteonecrosis. Osteomyelitis is a serious and potentially disabling condition but can be difficult to differentiate from benign conditions of SCD, such as vaso-occlusive crisis. Diagnosis of osteomyelitis requires careful evaluation of the clinical presentation, laboratory testing, and imaging. Treatment of osteomyelitis in patients with SCD may be medical or surgical, but considerations in antibiotic selection and management preoperatively and postoperatively must be taken to ensure optimal outcomes.

Pathophysiology

Sickle cell disease (SCD) is the most commonly inherited hematological disorder, affecting millions of patients worldwide. It is estimated that the overall prevalence of SCD in African-Americans is one in 365. This condition produces abnormal hemoglobin, which leads to the “sickling” of red blood cells. Patients frequently present with hemolytic anemia and microvascular occlusion leading to vaso-occlusive crisis (VOC). Patients with SCD are also at an increased risk of orthopaedic manifestations such as osteomyelitis, septic joint, or osteonecrosis. Osteomyelitis is one of the most serious and potentially disabling orthopaedic manifestations of SCD, but its differentiation from benign SCD conditions such as VOC can be difficult. This article aims to discuss the pathophysiology, clinical presentation, diagnosis, and management of osteomyelitis in the SCD population.
Sickle cell trait occurs in heterozygote carriers of this mutation. Carriers have relative protection against *Plasmodium falciparum* malaria fatality, explaining the high prevalence of the gene in geographic areas of endemic malaria. However, carriers of the sickle cell trait usually do not develop clinical manifestations of the illness. This review focuses on SCD, which is of autosomal recessive inheritance.

In SCD, the abnormal erythrocytes can precipitate acute episodic clinical events. The accumulation of sickle cells in the blood stream can occlude the microvasculature, leading to bone infarction and activation of inflammatory pathways. VOC, also known as sickle cell crisis, can affect multiple systems, including the splenic, hepatic, renal, nervous, and musculoskeletal systems (Figure 2). Children with SCD develop functional hyposplenia because of auto-infarction, which generally occurs before the age of five. This impairs the body’s immune response against encapsulated organisms. Combined with the presence of infarcted bone, sickle cell patients are found to be at a greater risk for osteomyelitis.

In the general population, *Staphylococcus aureus* (*S. aureus*) is the most common organism associated with osteomyelitis. In Africa and the Middle East, it is also the most common pathogen of osteomyelitis (39% and 62%, respectively) compared with other pathogens isolated from patients with SCD. However, in America, Gram-negative enteric bacilli such as *Salmonella spp.* (70%) are more commonly found in the SCD population than *S. aureus* (16.4%). It is postulated that these enteric bacteria arise from ischemic infarction of bowels during vaso-occlusive episodes.

### Clinical Manifestations

In the acute stage of presentation, VOC and osteomyelitis are nearly indistinguishable, although VOC is up to 50 times more common than osteomyelitis in patients with SCD. In both cases, patients may present with fever and a painful, swollen limb with limited range of motion. Usually, osteomyelitis affects the diaphysis of long bones, such as the femur and humerus, but it is possible for any other bone to be affected. Berger et al found that fever and pain identified for at least 24 hours...
before presentation and swelling of
the affected limb were important
predictors of osteomyelitis in children
with SCD. Their results also suggest
that patients with osteomyelitis were
less likely to have multiple painful
sites than those experiencing a vaso-
occlusive episode.

Laboratory testing is not always
reliable in distinguishing osteomyelitis
from VOC because both conditions
can be associated with leukocytosis
and elevated inflammatory markers
(C-reactive protein and erythrocyte
sedimentation rate).11 The benchmark in diagnosing osteomyelitis is
having a positive culture from either a
sample of bone, synovial fluid, or
blood.14 However, the absence of a
positive culture does not rule out the
possible diagnosis of osteomyelitis.8
Because obtaining bone cultures is
extremely invasive and blood cultures
are frequently falsely negative,8 inte-
grating imaging studies is crucial to
identify osteomyelitis in patients with
SCD. Timely identification of osteo-
myelitis is necessary to begin appro-
priate antibiotic therapy and prevent
the need for surgical intervention.

**Diagnosis**

OM is difficult to differentiate from
VOC in patients with SCD. Although
VOC is much more common, OM is
an important diagnosis which must
not be overlooked. Clinical features,
laboratory findings, and radiological
features must be used together to
guide further diagnostic tests and
management. The following modal-
ties can identify radiographic features
that may raise clinical suspicion of
OM.

**Plain Radiographs**

In the early stages of osteomyelitis and
VOC, plain radiographs are usually
found to be either normal or only
showing soft-tissue edema, periostitis,
or osteopenia.3,8 The lytic changes
suggestive of osteomyelitis lag at least
2 weeks behind the process of the
infection on radiographs.15 Thus, the
poor sensitivity and specificity for
early detection by plain radiography

**Figure 3**

Ultrasonography of the lateral soft-tissue of the hip showing a subcutaneous
collection measuring 8.4 cm by 2.4 cm. This collection was used as an indirect
indication of the presence of OM because it is likely to have formed secondary to
the infection.

**Figure 4**

Coronal T1 (A), coronal T1 postcontrast (B), and coronal short tau inversion-
recovery (C) images of the femur demonstrating extensive marrow edema with
associated serpiginous and tubular marrow enhancement in the distal femoral
metaphysis/diaphysis (solid arrows) with extensive associated periosteal
reaction (arrowhead), adjacent soft-tissue swelling, and edema (dashed
arrows). These findings are characteristic of osteomyelitis. The figure
reproduced with permission from Kosaraju et al.13
prompts the need for evaluation with other imaging modalities.\textsuperscript{11}

**Ultrasonography**

Ultrasonography is a rapid and non-invasive investigation that has the ability to show acute findings of extraosseous pathology and/or periosteal elevation in osteomyelitis.\textsuperscript{16} In patients with an elevated C-reactive protein and/or white cell count on admission, the sensitivity of ultrasonography has been shown to be as high as 76\% to detect osteomyelitis in SCD.\textsuperscript{11} Although subperiosteal fluid may also be found in VOC, it has been reported that a subperiosteal fluid collection $>4$ mm is a strong indicator of osteomyelitis (Figure 3).\textsuperscript{16} The mentioned findings are indirect signs of the presence of osteomyelitis but are effective tools when correlated with clinical evidence. With the expansion of ultrasonography as a low-cost and portable device, ultrasonography may be a useful modality for detecting early indirect signs of osteomyelitis in patients with SCD, especially in low-resource settings.

**MRI**

MRI is the imaging modality of choice for diagnosis of osteomyelitis\textsuperscript{17} because the sensitivity has been reported up to 100\% (Figure 4).\textsuperscript{18} Early pathological features, such as bone marrow edema, are detectable as early as 24 hours after infection begins.\textsuperscript{17} On MRI, bone marrow edema typically presents as a localized marrow abnormality of decreased signal on T1-weighted images and increased signal on T2-weighted images (Figure 4).\textsuperscript{15} Other secondary findings of osteomyelitis such as soft-tissue collections, cellulitis, and cortical bone sinus tracts also have similar MRI signalling characteristics (decreased on T1, whereas increased on T2).\textsuperscript{17} Used consecutively, MRIs may also be correlated with clinical evidence to evaluate the response to antibiotic therapy, without risk of ionising radiation.
Gadolinium enhancement can improve the accuracy of MRI because the regions of infection show substantial contrast enhancement after gadolinium administration. Unless contraindicated (ie, impaired renal function), gadolinium contrast imaging is typically performed with MRI to help identify and characterize complications such as abscesses or sinus tracts, which may be missed otherwise.

It is important to correlate the clinical presentation with the MRI findings because MRI is reported to have lower specificity than sensitivity (75% to 96%, vs 82% to 100%). This is because many of the MRI findings of OM and VOC overlap, and currently no reliable imaging parameter exists to effectively differentiate these diagnoses. MRI findings may overestimate the severity of the infection or may be indistinguishable from other pathologies such as malignancy. Finally, although MRI is a powerful diagnostic tool, it remains costly and may not be suitable for young children, patients with metal implants, or situations requiring imaging of large parts of the body.

**Radionuclide Imaging**

Radionuclide scans may be used in situations when the diagnosis of osteomyelitis remains unclear (Figure 5). Given the high diagnostic accuracy of MRI, it is much less commonly used. A summary of the available scans is provided in Table 1. Because there is a high dose of radiation encountered during nuclear medicine scanning, these scans should be reserved in practice for specific cases in which the benefits outweigh the potential harm.

Although OM and VOC might be difficult to distinguish based on clinical pictures in patients with SCD, a combination of the clinical features, laboratory, and radiological workups all together will help clinicians distinguish one diagnosis from the other (Table 2).

**Medical Management**

Initial management typically includes IV hydration, oxygenation, and pain control until the diagnosis of OM has been made. Unless the patient shows signs of sepsis and hemodynamic instability, appropriate cultures should be obtained before administrations of antibiotics to increase the likelihood of obtaining a pathogen. Empiric antibiotics can then be discontinued if the diagnosis of OM is ruled out.

In general, the typical duration of parenteral antibiotic treatment of osteomyelitis runs 4 to 6 weeks. Trials of extended courses of either parenteral or oral antibiotics have not suggested improved outcomes compared with 6 weeks of therapy. If patients are...
deemed to be stable enough for discharge, outpatient intravenous antibiotics may be administered through a peripherally inserted central catheter line.

As described previously, *S aureus*, Salmonella, and other gram-negative bacilli are the most commonly isolated organisms from individuals with osteomyelitis in the SCD population. Ideally, the results of a positive blood culture, biopsy, or aspiration should be used to direct the choice of antibiotic. Currently, there is a paucity of literature to

---

**Table 2**

| Clinical Features and Findings Differentiating VOC From Osteomyelitis |
|---------------------------------------------------------------|
| **Factor** | **VOC** | **Osteomyelitis** |
| Prevalence | 50x more common than osteomyelitis | — |
| History and physical examination | | |
| Fever | Fever (>38.0°C) is possible | Fever (>38.0°C) more likely to be identified for 24 hours before presentation |
| Location of pain | May have multiple sites of pain | More likely to have pain in a single area, usually the diaphysis of a long bone |
| Joint appearance | Joint swelling is possible | More likely to present with joint swelling |
| Laboratory testing | | |
| Leukocytes | Normal to mildly elevated | May be elevated |
| Inflammatory markers (CRP, ESR) | Normal to mildly elevated | Although not specific for osteomyelitis, more prominent elevations in CRP and ESR are found in osteomyelitis |
| Cultures | — | Benchmark diagnosis is a positive culture from bone, blood or synovial fluid |
| Imaging | | |
| Plain radiograph | Usually normal, but both conditions may show soft-tissue edema, periostitis, or osteopenia | |
| MRI | — | Localized marrow abnormality of decreased marrow signal on T1-weighted images and increased signal on T2-weighted images |

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VOC = vaso-occlusive crisis

**Table 3**

| Preferred First-Line Antibiotic Regimens, Based on the Causative Organism |
|--------------------------------------------------------------------------|
| **Organism** | **Preferred first-line regimen** |
| Anaerobes | Clindamycin 600 mg IV q6h, or Ticarcillin/clavulanate, 3.1 g IV q4h |
| Enterobacteriaceae, quinolone-sensitive | Ciprofloxacin 400 mg IV q8-12h |
| Enterobacteriaceae, quinolone-resistant | Piperacillin/tazobactam, 3.375 g IV q6h, or Ticarcillin Clavulanate, 3.1 g IV q4h |
| *Pseudomonas aeruginosa* | Cefepime, 2 g IV q8-12h, with ciprofloxacin 400 mg IV q8-12h |
| *S aureus*, methicillin-sensitive | Cefazolin, 1-1.5 g IV q6h, or Nafcillin or Oxacillin, 1-2 g IV q4h |
| *S aureus*, methicillin-resistant | Vancomycin 1g IV q12h, or if allergic, Linezolid 600 mg IV q12h |
| Streptococcus species | Penicillin G, 2-4 million units IV q4h |

Adapted from Hatzenbuehler et al (2011). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
direct antibiotic selection for patients with SCD with osteomyelitis, as per the 2016 Cochrane review.22 Thus, discussion with an infectious disease specialist to determine the choice of antimicrobial therapy and length of treatment is imperative and performed on a case-by-case basis.22 Almeida and Roberts8 recommended first-line treatment of confirmed or suspected osteomyelitis to be a third-generation cephalosporin to ensure coverage of the aforementioned organisms. Another reasonable combination for empiric antibiotic treatment is a combination of vancomycin and ciprofloxacin.23 Further studies are needed to clarify the most effective antibiotic selection for osteomyelitis in the SCD population. Examples of antibiotic regimes for the common offending bacteria of osteomyelitis in SCD have been provided in Table 3.

Surgical Management
As stated above, MRI can be useful for evaluating the response of osteomyelitis to antibiotic treatment. Remaining or nonresponsive nidi of infection, or areas of necrotic bone, require surgical débridement, followed by antimicrobial therapy.23 Evaluation of the patient and their most recent MRI by an orthopaedic surgeon is essential for optimal outcomes. In compromised hosts, surgical management may not be feasible in all cases. If the host is severely compromised and the risk of operation outweighs the benefits, the option for treatment may only be nonsurgical (such as antibiotic suppression). In extreme cases, amputation may be necessary as a life-saving intervention.15

Surgical treatment of osteomyelitis includes surgical débridement to remove necrotic and infected material and is followed by soft-tissue coverage using either direct closure or flap coverage. Intraoperative cultures are typically sent to confirm the offending pathogen. If a patient commenced empiric antibiotic therapy and is no longer acutely ill (ie, no evidence of soft-tissue infection or sepsis), it is optimal for antibiotics to be discontinued for at least two weeks before débridement. This allows for greater accuracy in microbiologic identification.15

Débridement of bone is performed until punctate bleeding is found, also known as the “paprika sign.”26 In
immunocompromised patients such as the SCD population, margins of at least 5 mm are recommended to reduce the risk of recurrence.\textsuperscript{15} Within the area of débridement, local antimicrobials may be placed directly to the site of infection via absorbable (ie, calcium sulfate beads) or nonabsorbable carriers (ie, polymethyl methacrylate).\textsuperscript{27} These are used to sterilize the area and temporarily maintain the dead space but eventually can be replaced after 2 to 4 weeks with cancellous bone graft.\textsuperscript{15} During the process of healing, skeletal stability may need to be increased to reduce stress on the affected bony area and surrounding soft tissues. In general, external fixation is recommended because internal fixation has a tendency to become secondarily infected.\textsuperscript{15}

After débridement, adequate soft-tissue coverage of the bone may be done via either direct closure or flap coverage.\textsuperscript{15} Direct closure is preferred when surgical intervention results in a minimal defect, in which the bone and soft tissues can be enclosed easily. However, with large soft-tissue defects or when there may be exposed bone, joint, or tendons, local muscle flaps or a free flap can improve the healing environment by improving vascularization. This brings natural host defense mechanisms and also improves antibiotic delivery.\textsuperscript{15} When flap coverage is necessary, consultation with plastic surgery is suggested for optimal management. Complete wound closure is always recommended because healing by secondary intention may cause avascular scar tissue to develop in the defect.\textsuperscript{15}

More recently, the induced membrane (Masquelet) technique has been introduced for the management of bone defects after débridement of osteomyelitis.\textsuperscript{28,29} First, a cement spacer is placed into the defect. The spacer is made of polymethyl methacrylate, which serves to prevent scar tissue from developing in the defect, and inducing osteogenesis through releasing osteoprogenitor cells. A second operation is performed 6 to 8 weeks later to carefully incise the induced membrane and replace the spacer with autologous bone graft (Figure 6).\textsuperscript{28} Giannoudis et al\textsuperscript{28} reported harvesting this graft material from the femoral intramedullary cavity with a reamer/irrigator/aspirator (RIA) device. Because it is a relatively novel technique, further studies are necessary to determine the efficacy of the Masquelet technique in achieving bone union and eradication of infection.

A systematic review by Morelli et al\textsuperscript{29} found that almost 50% of patients had complications (superficial or deep surgical site infections) and that 18% of patients required reintervention (because of persistence of infection or nonunion).

### Perioperative Considerations

Orthopaedic intervention in the SCD population carries a higher risk of complications in comparison with patients without SCD undergoing similar procedures.\textsuperscript{31}

Preoperatively, evaluation of patients for transfusion includes serial hemoglobin, hemoglobin S level (HbS%), renal function, liver function, and oxygen saturation.\textsuperscript{32} Simple transfusion therapy (also known as conservative transfusion) is used to increase hemoglobin levels to 10 g/dL using sickle-negative blood.\textsuperscript{31} This has been shown to provide similar outcomes as aggressive transfusion, which targets to decrease HbS% to <30%.\textsuperscript{31} Exchange transfusion is another preoperative transfusion technique, which involves the removal the patient’s sickled blood and replacing it with donor packed red blood cells. Exchange transfusion has been found to have similar outcomes as simple transfusion but requires a larger amount of blood to be transfused and results in a higher rate of transfusion-related complications.\textsuperscript{33}

With general anesthesia, patients with SCD have an increased risk for acute chest syndrome (ACS) and VOC.\textsuperscript{32} ACS is a life-threatening
condition secondary to occlusion of the pulmonary vasculature, which is defined as fever and respiratory symptoms with newfound pulmonary infiltrates found on chest radiograph. Initial therapy requires fluid management, supplementary oxygen, pain management, bronchodilators, and empiric antibiotics. In cases of worsening hypoxemia despite supplemental oxygen, urgent transfusion therapy is warranted. Perioperatively, patients with SCD should have careful monitoring of cardiac rhythm, blood pressure, and oxygen saturation. Because they are also at an increased risk for hypothermia, intraoperative warming measures (ie, warming blanket) are also of benefit.

After surgery, patients with SCD are encouraged to use incentive spirometry and chest physiotherapy to prevent ACS. Appropriate IV antibiotics are also given, particularly based on the sensitivities of the organisms of the infection. Finally, supplemental oxygen and IV hydration are imperative to prevent the occurrence of vaso-occlusive crisis. Resuming regularly prescribed medications, such as hydroxyurea or L-glutamine, are to be considered at this time as well. Yawn et al recommended that during hospitalization, individuals with SCD should continue on their usual dose of hydroxyurea, unless they are found to have developed secondary cytopenia or are pregnant/breastfeeding. We (as authors) preferred certain algorithm that illustrated in the Figure 7 to manage osteomyelitis in SCD.

Summary

Osteomyelitis is serious medical condition that can be difficult to identify, especially in patients with SCD. Although VOC is a much more common presentation, clinicians must consider the possibility of osteomyelitis when evaluating patients with SCD who present with fever and a swollen limb. Advancements in imaging such as MRI and radionuclide scanning may be helpful in differentiating the two conditions. If infection remains present despite antibiotic therapy, adequate surgical management is necessary to ensure optimal outcomes.

References

1. Ware RE, de Montalember M, Tsuhlolo L, Abboud MR: Sickle cell disease. Lancet 2017;390:311-323.
2. Hassell K: Population estimates of sickle cell disease in the U.S. Am J Prev Med 2010; 38:S512-S521.
3. Vanderhave K, Perkins C, Scannell B, Brighton B: Orthopaedic manifestations of sickle cell disease. J Am Acad Orthop Surg 2018;26:94-101.
4. Berger F, Saunders N, Wang L, Friedman JN: Sickle cell disease in children: Differentiating osteomyelitis from vaso-occlusive crisis. Arch Pediatr Adolesce Med 2009;163:251-255.
5. Rees DC, Williams TN, Gladwin MT: Sickle-cell disease. Lancet 2010;376: 2018-2031.
6. Archer NM, Petersen N, Clark MA, Buckee CO, Childs LM, Duraisingh MT: Resistance to Plasmodium falciparum in sickle cell trait erythrocytes is driven by oxygen-dependent growth inhibition. Proc Natl Acad Sci U S A 2018;115:7350-7355.
7. Brousse V, Buffet P, Rees D: The spleen and sickle cell disease: The sickled (led) spleen. Br J Haematol 2014;166:165-176.
8. Almeida A, Roberts I: Bone involvement in sickle cell disease. Br J Haematol 2005;129: 482-490.
9. Thanii LO: Bacterial osteomyelitis in major sickling haemoglobinopathies: Geographic difference in pathogen prevalence. Afr Health Sci 2006;6:236-239.
10. Burnett MW, Bass JW, Cook BA: Etiology of osteomyelitis complicating sickle cell disease. Pediatrics 1998;101:296-297.
11. Inusa B, Oyewo A, Brokke F, Santhukumar G, Jogeessvaran K: Dilemma in differentiating between acute osteomyelitis and bone infarction in children with sickle cell disease: The role of ultrasound. PLoS One 2013;8:e63001.
12. Skaggs D, Kim S, Greene N, Harris D, Miller J: Differentiation between bone infarction and acute osteomyelitis in children with sickle-cell disease with use of sequential radionuclide bone-marrow and bone scans. J Bone Joint Surg Am 2001;83: 1810-1813.
13. Kosaraju V, Harwani A, Partovi S, et al: Imaging of musculoskeletal manifestations in sickle cell disease patients. Br J Radiol 2017;90:20160130.
14. Delgado J, Bedoya M, Green A, Jaramillo D, Ho-Fung V: Utility of unenhanced fat-suppressed T1-weighted MRI in children with sickle cell disease—Can it differentiate bone infarcts from acute osteomyelitis? Pediatr Radiol 2015;45:1981-1987.
15. Calhoun J, Manring M: Adult osteomyelitis. Infect Dis Clin N Am 2005; 19:765-786.
16. William RR, Hussein SS, Jeans WD, Wali YA, Lamki ZA: A prospective study of soft-tissue ultrasonography in sickle cell disease patients with suspected osteomyelitis. Clin Radiol 2000;55:307-310.
17. Lee YJ, Sadigh S, Makad K, Kapse N, Rajeswaran G: The imaging of osteomyelitis. Quant Imaging Med Surg 2016;6:184-198.
18. Pineda C, Espinosa R, Pena A: Radiographic imaging in osteomyelitis: The role of plain radiography, computed tomography, ultrasonography, magnetic resonance imaging, and scintigraphy. Semin Plast Surg 2009;23:80-89.
19. Malikus D, Jonkus M, Kupionis G, et al: The accuracy of different imaging techniques in diagnosis of acute hematogenous osteomyelitis. Medicina (Kaunas) 2009;45:624-631.
20. Berbari EF, Kanj SS, Kowalski TJ, et al: Infectious Diseases Society of America clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 2015;61:26-46.
21. Roblot F, Besnier JM, Juhel I, et al: Optimal duration of antibiotic therapy in vertebral osteomyelitis. Semin Arthritis Rheum 2007;36:269-277.
22. Marti-Carvajal AJ, Aguera-Perez LH: Antibiotics for treating osteomyelitis in people with sickle cell disease. Cochrane Database Syst Rev 2016;11:CD007175.
23. George A, DeBaun MR, DeBaun MR: Acute and chronic bone complications of sickle cell disease. UpToDate, 2019. https://www.uptodate.com/contents/acute-and-chronic-bone-complications-of-sickle-cell-disease.
24. Hatzenbuehler J, Pulling T: Diagnosis and management of osteomyelitis. Am Fam Physician 2011;84:1027-1033.
25. Karamis EM, Matthaiou DK, Moraitis LI, Falagas ME: Fluoroquinolones versus beta lactam based regimens for the treatment of osteomyelitis: A meta-analysis of randomized controlled trials. Spine (Phila Pa 1976) 2008;33:E297-E304.
26. Cierny G, III, Mader JT: The surgical treatment of adult osteomyelitis. In: Evarts September 2020, Vol 4, No 9
CMC, ed. *Surgery of the musculoskeletal system*. New York, NY, Churchill Livingstone, 1983, pp 15-35.

27. Hake ME, Young H, Hak DJ, Stahel PF, Hammerberg EM, Mauffrey C: Local antibiotic therapy strategies in orthopaedic trauma: Practical tips and tricks and review of the literature. *Injury* 2015;46:1447-1456.

28. Giannoudis PV, Harwood PJ, Tosounidis T, Kanakaris NK: Restoration of long bone defects treated with the induced membrane technique: Protocol and outcomes. *Injury* 2016;47:S53-S61.

29. Morelli I, Drag L, George DA, Gallazzi E, Scarponi S, Romano CL: Masquelet technique: Myth or reality? A systematic review and meta-analysis. *Injury* 2016;47:S68-S76.

30. Han W, Shen J, Wu H, Yu S, Fu J, Xie Z: Induced membrane technique: Advances in the management of bone defects. *Int J Surg* 2017;42:110-116.

31. Vichinsky EP, Neumayr LD, Haberkern C, et al: The perioperative complication rate of orthopedic surgery in sickle cell disease: Report of the National Sickle Cell Surgery Study Group. *Am J Hematol* 1999;62:129-138.

32. Sathappan SS, Ginat D, Di Cesare PE: Multidisciplinary management of orthopedic patients with sickle cell disease. *Orthopedics* 2006;29:1094-1101.

33. Alotaibi GS, Alséleh K, Bolster L, McMurry MS, Wu C: Preoperative transfusion in patients with sickle cell disease to prevent perioperative complications: A systematic review and meta-analysis. *Hematology* 2014;19:463-471.

34. Hammer M, Geier KA, Aksoy S, Reynolds HM: Perioperative care for patients with sickle cell who are undergoing total hip replacement as treatment for osteonecrosis. *Orthop Nurs* 2003;22:384-397.

35. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al: Management of sickle cell disease: Summary of the 2014 evidence-based report by expert panel members. *JAMA* 2014;312:1033-1048.