11. BONE COMPLICATIONS

Introduction

In patients with sickle cell disease (SCD) presenting with bone pain, clinicians must distinguish between common causes, including acute vaso-occlusive crisis (VOC), osteomyelitis (OM), and avascular necrosis (AVN), while also considering more rare complications such as abscesses, myositis, or septic arthritis. It is useful to know that bone pain in SCD is much more likely to be due to VOC than to OM. In one pediatric series, VOC was at least 50 times more likely.[1]

A thorough evaluation begins with assessing historical features of the pain. If the onset of symptoms was acute, it may be suggestive of VOC or OM, versus the chronic pain and disability caused by AVN. Concurrent infectious symptoms (e.g., fever, rigors) may suggest OM. Any prior history of bone complications can also guide further investigations.

Physical examination should include a musculoskeletal examination, targeting the joint or other location of symptoms. Selection of appropriate laboratory investigations and imaging should be guided by clinical suspicion.

a. Acute Vaso-occlusive Crisis

Principles

- To recognize clinical syndromes suggestive of acute vaso-occlusive crisis.
- To undertake appropriate investigations to diagnose acute vaso-occlusive crisis.
- To provide supportive therapy in acute vaso-occlusive crisis, including appropriate pain management.
- To prevent acute vaso-occlusive crisis.

Recommendations

- The clinician should take a careful history of the pain, including onset, location, and quality
- Imaging studies are only necessary if there is concern that the pain may be due to a cause other than acute vaso-occlusive crisis
- Pain management with opiate analgesia – medication, dose, and route must be selected based on the severity of pain
- Adjunctive use of non-steroidal anti-inflammatory agents
- Respiratory status should be monitored in patients receiving high doses of opiates
- Active hydration with frequent reassessments; oral fluid is preferable to intravenous if the patient is able and motivated to drink
- Supplemental oxygen (if hypoxemic)
- During an episode of VOC, patients should be monitored clinically for onset of acute chest syndrome
- There is no role for red blood cell transfusion or empiric antibiotic therapy in an uncomplicated vaso-occlusive episode
- Upon resolution of pain episode, the patient should be assessed for chronic hydroxyurea therapy to prevent recurrent episodes

Further discussion of analgesia in vaso-occlusive crisis can be found in Part II, section 1 on Pain.

Background

Vaso-occlusion in patients with SCD causes infarction leading to bone pain. Common locations for acute VOC include the long bones, ribs, sternum, spine, and pelvis, although infarcts can occur in any bone in the body.[2] In young children, dactylitis (painful swelling of the fingers or toes) is a common presentation, due to infarction of the small bones in the hands or feet.

Dactylitis: Microinfarcts in the small bones of the hands and feet can lead to tenderness and swelling of the digits, known as dactylitis or "hand and foot syndrome". This typically occurs in infants and young children under the age of 5, in whom there is still hematopoietic bone marrow in the small bones. In a prospective study of 233 children with sickle cell anemia (HbSS), 45% of children had experienced dactylitis between birth and 2 years of age. Episodes were more common during the colder months of the year. Affected patients had lower fetal hemoglobin (HbF) and higher reticulocytes than unaffected children.[3] Dactylitis in infancy helps to predict a more severe course later in life.[4] Patients present with painful, often symmetrical swelling of the hands or feet, often accompanied by mild skin erythema and low-grade fever. In this clinical setting, the differential diagnosis of osteomyelitis should be considered, although osteomyelitis affecting several digits would be unusual. Dactylitis should be treated in the same manner as other VOCs – with supportive care and pain management. Hydroxyurea should be considered in infants and children with SCD to prevent dactylitis and other end-organ complications.[5]

The clinical presentation of a VOC of bone is dominated by the acute onset of deep-seated pain, often described by the patient as "typical sickle cell pain." Mild erythema and warmth, as well as local tenderness, are usually present. Many patients also have a low-grade fever. Pain can vary from mild (i.e., barely interfering with normal lifestyle) to excruciating.

Diagnosis of acute VOC is generally based on the findings of clinical assessment. Laboratory investigations may reveal non-specific elevations of the white blood cell count and/or erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Abnormalities on plain x-ray, radioisotope bone scan, and radiolabelled leukocyte scan are often difficult to distinguish from those seen in OM. Ultrasound may reveal a subperiosteal fluid collection, which is typically smaller in VOC (<10 mm) than in OM (>10 mm). Subperiosteal fluid aspirate is likely to be hemorrhagic with a negative culture (versus turbid or purulent fluid with a positive culture in OM).[6]

Empiric treatment in presumed acute VOC includes active hydration, and supplemental oxygen (if hypoxemic). Symptom management strategies include heat packs applied to the painful site. Analgesia with opiates should be tailored to the severity of pain; for example, oral morphine for mild pain versus frequent intravenous opioid (ideally via PCA) or continuous infusion for severe pain. Anti-inflammatory medications may be used adjunctively. During an episode of VOC, patients should be monitored clinically for onset of acute chest syndrome, which can develop due to fat embolism following bone infarction.

Chronic hydroxyurea therapy can prevent VOC in patients with HbSS or patients with HbS-beta^0-thalassemia with repeated episodes. (*For more detailed discussion, see Part I, section 1 on Hydroxyurea*)

b. Osteomyelitis

Principles

- To recognize clinical syndromes suggestive of osteomyelitis.
- To undertake appropriate investigations to diagnose osteomyelitis.
- To provide appropriate treatment.
- To monitor for improvement while on therapy or following treatment.

Recommendations

- Consider osteomyelitis in the differential diagnosis of a patient with bone pain that is "not like their typical sickle pain", particularly in the presence of other clinical or laboratory markers of infection.
- Ultrasound may be helpful in evaluating for osteomyelitis.
- Definitive diagnosis requires aspirate of periosteal fluid collection or bone biopsy, performed by an Orthopedic specialist or Interventional Radiology expert.
- Treatment should include a minimum of six weeks of antibiotics to cover the cultured organisms.

- Oral therapy should only be used when the organism is found to have good sensitivity and adequate serum bactericidal levels can be attained.
- Consultation with an Infectious Disease expert may be beneficial in determining optimal choice and duration of antibiotics.
- The role for operative decompression as part of first-line therapy is unclear; surgical debridement may be beneficial in cases that do not improve as expected on antibiotics.

Background

Mechanisms responsible for the increased risk of osteomyelitis in SCD likely include: hyposplenism, impaired complement activity, bowel infarction leading to migration of bowel flora to the bloodstream, and the presence of infarcted or necrotic bone. Typical organisms include *Salmonella* species, *Staphylococcus aureus* and Gram-negative enteric bacilli.[7,8]

Elevated temperature may be suggestive of OM or other infectious etiology, while other abnormalities in vital signs (e.g., tachycardia, hypotension) potentially indicate progression to sepsis.

Leukocytosis and increased ESR or CRP are non-specific laboratory findings that may be present in both infectious and non-infectious processes. A definitive diagnosis of OM in SCD requires positive cultures from blood, subperiosteal fluid collection, or bone.

Plain radiography, radioisotope bone scanning, and radio-labelled leukocyte scanning are not useful in the routine diagnostic evaluation of bone pain in SCD, as these modalities can detect acute infarction, but changes are often difficult to distinguish from those seen in OM.[9]

Ultrasonography is a rapid, simple, and non-invasive modality that is moderately sensitive for detecting acute osteomyelitis.[10] The main ultrasonographic finding in OM is subperiosteal fluid. Larger fluid collections ([>4 mm][10] or [>10 mm][6]) are more characteristic of OM versus smaller collections that may be seen in VOC. Aspiration of subperiosteal fluid under ultrasound guidance may aid diagnosis; the aspirate is typically hemorrhagic in VOC and turbid or purulent, with positive cultures in OM. Diagnosis based on ultrasound has led to successful management in a prospective, pediatric study.[32] In a retrospective study comparing OM patients with control cases presenting with VOC, 76% of OM patients had periosteal elevation and/or fluid collection on initial ultrasound, and 84% of patients had a positive ultrasound at some time during their hospital stay. Although 9% of patients with VOC had an initial positive ultrasound, all ultrasounds demonstrated small fluid collections (<4 mm), and repeat ultrasounds were all negative. Mean CRP levels and white blood cell (WBC) count at presentation were significantly higher in the OM group.[11]

Magnetic resonance imaging (MRI) can be useful in the diagnosis of OM. As with other imaging modalities, there is overlap between the changes seen in infection and infarction. Although still not 100% specific for differentiating OM from VOC,[12] gadolinium enhancement improves the accuracy of MRI.[13]

OM must be treated with at least 6 weeks of antibiotic therapy, tailored to the organism identified. If culture sensitivities offer the option of oral antibiotics, oral therapy may be considered only if adequate serum bactericidal levels can be attained. Assessment by an Infectious Disease and/or Orthopedic specialist should be performed, if possible. In more complicated or refractory cases, adjunctive therapies may include operative decompression or drainage of any fluid collections identified on imaging. Infection resolved in twenty-nine of thirty affected bones in a study of SCD patients with osteomyelitis confirmed on bone culture and treated with operative decompression and a minimum of six weeks of parenteral antibiotics (97%).[7]

MRI may be a useful imaging modality for monitoring response to therapy.[14]

c. Avascular Necrosis

Principles

- To recognize clinical syndromes suggestive of avascular necrosis.
- To undertake appropriate investigations to diagnose avascular necrosis.
- To provide appropriate supportive care in early avascular necrosis.
- To identify progression to bone deformity and consider the role for surgical intervention.

Recommendations

- Consider the possibility of AVN in any patient with ongoing, localized bone pain. Clinicians should have a high degree of suspicion for AVN in patients with pain and/or decreased range of motion in the hip.
- MRI may be performed to detect early disease.
- Supportive care should include adequate analgesia.
- A physiotherapist and/or Orthopedic specialist with interest in SCD may be consulted to advise on appropriate exercises and parameters for physical activity (see Figure 1).
- There is no evidence currently for the use of hip core decompression.
- Patients with advanced femoral- or humeral-head disease should be evaluated by an Orthopedic specialist with interest in SCD for possible arthroplasty.
- Any arthroplasty should be performed with special attention to decreasing the risk of perioperative complications ( ).

Background

Osteonecrosis (avascular necrosis, AVN) occurs when sickling of cells in the bone microcirculation leads to infarction of the bone marrow and death of osteoblasts. The most common locations for AVN are the femoral and humeral heads, with a prevalence of 10% and 6%, respectively, in a group of patients with SCD who are over the age of 5 years old[15,16]; however, prevalence is higher in older groups.[17,18]

Cohort studies have demonstrated that AVN may be asymptomatic when originally detected,[18] but symptoms and bone deformity often progress rapidly over time.[19] Clinical symptoms may include pain, deformity, limb shortness, stiffness, or limited range of motion of the joint.

Diagnosis is based on imaging. MRI is the most sensitive method of detection, and is, therefore, particularly helpful for early detection of disease. Characteristic findings on plain x-ray make it a useful modality in advanced disease.[8] Staging of disease severity can be performed using the Ficat and Arlet[20] or Steinberg systems.[21,22]

Initial treatment is conservative: bed rest with progressive weight bearing in the case of hip AVN (see Figure 1) or rest with part-time shoulder splinting in the case of shoulder AVN. Symptomatic treatment with analgesics is crucial. Application of heat, such as use of heating pads or whirlpools may also help to improve symptoms.[23]

Unfortunately, no additional intervention has been shown definitively to slow progression of early disease. Hip core decompression followed by physiotherapy was not superior to physiotherapy alone in a prospective, multicenter study. The study suffered several limitations, however; it was inadequately powered with short duration of follow-up (3 years).[24]

AVN of the hip can lead to femoral-head collapse, which requires hip arthroplasty.[18,19] Surgery should be performed in a specialized centre, with special attention to minimizing the risk of perioperative complications (*see "Peri-operative Care" section of current guidelines*). Revision is frequently required.[16,25]

Joint replacement is also the treatment of choice in advanced shoulder AVN. Patients have variable outcomes, however, in terms of function and pain relief with this procedure.[26,27]

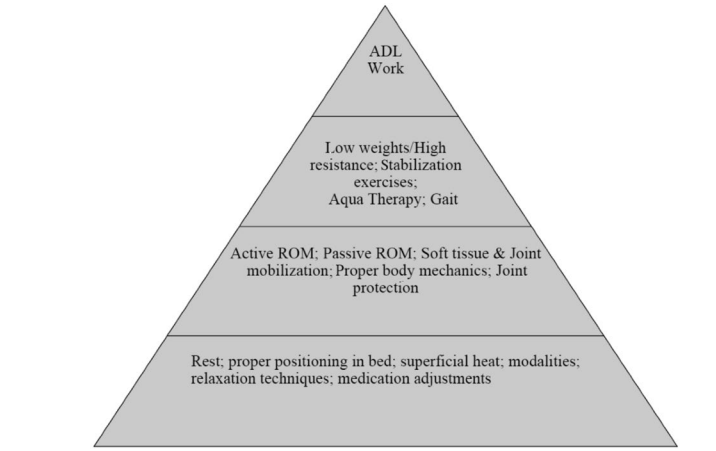

Fig. 1. A therapeutic treatment pyramid.

ADL: activities of daily living; ROM: range of motion

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d. Low Bone Mineral Density

Principles

- To recognize low bone mineral density (BMD) in patients with SCD.
- To assess for and manage underlying risk factors for low bone mineral density.
- To provide appropriate pharmacologic and non-pharmacologic therapy to improve bone mineral density in patients with low bone mineral density.

Recommendations

- All patients should have height, weight, and BMI measured, at least annually.
- History of fractures should be recorded.
- 25-hydroxy-vitamin D levels should be assessed at baseline, starting in infancy.
  - If levels are normal, they should be reassessed regularly (e.g., every 1 to 2 years).
  - If levels are low, supplementation should be prescribed according to current guidelines (e.g., vitamin D 1,000 to 2,000 IU daily).
- All patients should have a baseline Dual-energy X-ray absorptiometry (DXA) scan, repeated at intervals appropriate to their risk category (e.g., every 5 years for low risk and every 1 to 3 years for patients with moderate- and high-risk T-scores who are being actively managed).
- Non-pharmacologic approaches to building bone strength include resistance training and/or weight-bearing aerobic exercise, and a diet high in calcium-rich foods.
- Intake of calcium and vitamin D should be reviewed, with supplementation doses selected based on dietary intake, serum vitamin D levels, and risk level.
- Patients with osteoporosis (defined T-score ≤-2.5), should be assessed by an Endocrinologist or Osteoporosis specialist, with careful consideration of the role of anti-resorptive therapies.

Background

Based on clinical experience and a small number of studies, children and adults with SCD are known to have higher rates of low bone mineral density (BMD) than the general population. As in other patient groups, low BMI and low vitamin D levels are risk factors for low BMD.[28,29] Other potential contributing variables include lower

hemoglobin level, higher ferritin, male gender, and low serum zinc concentration.[29,30] Further study is required to clearly elucidate the pathogenesis of disproportionately high rates of reduced BMD in patients with SCD. The natural history, fracture risk, and specific therapeutic approach to low BMD in SCD also warrant further investigation.

In the absence of strong evidence to guide therapeutic decision-making, guidelines such as the "2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada"[31] should be followed. Non-pharmacologic approaches to building bone strength include resistance training and/or weight-bearing aerobic exercise, and a diet high in calcium-rich foods. Intake of calcium and vitamin D should be reviewed, with supplementation doses selected based on dietary intake, serum vitamin D levels, and risk level. Pharmacologic therapy should be considered for all patients with osteoporosis (defined as a T-score ≤-2.5), in the context of their other risk factors. Assessment by an Endocrinologist or Osteoporosis specialist may be beneficial.

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