REVIEW ARTICLE

Management of Charcot Arthropathy

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ABSTRACT

Charcot arthropathy (Charcot neuroarthropathy, diabetic neuropathic osteoarthropathy, or neuropathic arthropathy) remains a poorly understood disease. The etiology of Charcot remains unknown, although it has been suggested that it is triggered by the occurrence of inflammation in the foot of a susceptible individual, and that the inflammation results in increased osteoclastic activity, although recent research has improved our level of knowledge regarding its management. It has been well established that this complication of diabetes mellitus severely reduces the overall quality of life and dramatically increases the morbidity and mortality of patients. The goal of this study is to evaluate the modern concepts of Charcot arthropathy and to integrate a perspective of management.

Keywords: Diabetes mellitus, Charcot arthropathy, Diagnosis, Current treatments

INTRODUCTION

Neuropathic arthropathy (or neuropathic osteoarthropathy), also known as Charcot joint (often "Charcot foot"), refers to progressive degeneration of a weight bearing joint, a process marked by bony destruction, bone resorption, and eventual deformity. (Figure1, 2) Onset is usually insidious and it can occur in different parts of body. (Table1) Onset occurs after the patient has been diabetic for 15 to 20 years, usually at the age of 50 or older. The disorder occurs at the same rate in men and women. If this pathological process continues unchecked, it could result in joint deformity, ulceration and/or superinfection, loss of function, and in the worst case scenario, amputation or death. Early identification of joint changes is the best way to limit morbidity. Charcot arthropathy has been associated with leprosy, toxic exposure, syringomyelia, poliomyelitis, rheumatoid arthritis, multiple sclerosis, congenital neuropathy, and traumatic injury [1, 2] . The obesity epidemic is increasing the incidence of Charcot foot (Figure 3). However, diabetes mellitus has become the most common etiology in the modern era.[3]Charcot foot can occur in a diabetic who has neuropathy (nerve damage) in the foot that impairs the ability to feel pain. Charot foot typically occurs following a minor injury, such as a sprain or stress fracture. The prevalence of Charcot arthropathy ranges from 0.1% to as high as 13%. In patients with diabetes, the incidence of acute Charcot arthropathy of the foot and ankle ranges from 0.15-2.5% [4]. Epidemiologic studies do not distinguish between acute and postacute disease. Bilateral disease occurs in less than 10% of patients. Recurrence of disease occurs in less than 5% of patients. Some studies indicate that men and women are equally affected, while others report a 3:1 predilection for males.[5] Charcot fractures that are not identified and treated properly may progress to marked joint deformity and to skin ulceration over a bony prominence. The ulceration can result in a severe infection, which may lead to amputation of the extremity[6]. Another complication of Charcot arthropathy is foot collapse leading to the formation of a clubfoot. Another commonly seen deformity is the rocker-bottom foot, in which collapse and inversion of the plantar arch occurs. Other complications include the ossification of ligamentous structures, the formation of intra-articular and extra-articular

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exostoses, the collapse of the plantar arch, and the development of osteomyelitis.[6, 7]

Diagnosis

The natural history of the joint destruction process has a classification scheme of its own, offered by Eichenholtz decades ago.(Table 2) The initial manifestations of the Charcot foot are frequently mild in nature, but can become much more pronounced with unperceived repetitive trauma. Diagnostic clinical findings include components of neurological, vascular, musculoskeletal, and radiographic abnormalities. There have been no reported cases of Charcot neuropathic osteoarthropathy (CN) developing in the absence of neuropathy.[8, 9]

Imaging of the Charcot foot: Radiographs are the primary initial imaging method for evaluation of the foot in diabetic patients. Easily available and inexpensive, they provide information on bone structure, alignment, and mineralization. X-rays may be normal or show subtle fractures and dislocations or later show more overt fractures.[10]As with ultrasonography, Computed Tomography (CT) scanning has no significant role in the diagnosis of neuropathic arthropathy. However, CT scans may be helpful in evaluating cortical destruction, sequestra, and intraosseous gas. On T1-weighted (Magnetic Resonance Imaging) MRIs, joints involved in neuropathic arthropathy (Charcot joint) appear diffusely swollen and demonstrate low signal intensity. The fat plane adjacent to the skin ulceration appears hypointense; when the joints are infected with a gas-producing organism, areas showing a loss of signal intensity are seen. After the intravenous administration of a gadolinium-based contrast agent, the inflammatory mass enhances and demonstrates central non enhancing necrotic debris. The role of radioisotopic studies is to detect osteomyelitis in a neuropathic joint.[11] Three-phase phosphate scintigraphy has a high sensitivity (85%) but a low specificity (55%) because of bone remodeling of other causes. Studies using uptake of the gallium-67 (67 Ga) citrate have a high false-positive rate. Scanning using indium-111 (111 In)–labeled leukocytes has the highest sensitivity (87%) and specificity (81%) for detecting osteomyelitis in a neuropathic foot. The role of positron emission tomography (PET) scanning with fluorodeoxyglucose (FDG) is promising.[12]One study has shown a valuable role of FDG-PET scanning in the setting of neuroarthropathic arthropathy (Charcot joint) by reliably differentiating it from osteomyelitis.[13]

Differential diagnosis

While cellulitis may seem to be the likely diagnosis, if a patient with long-standing diabetes, a history of poor glycemic control, and peripheral neuropathy presents with a red, hot, swollen foot with no history of open ulceration, then Charcot neuroarthropathy should be at the top of the list in the differential diagnosis. Other possibilities include osteomyelitis, acute gout, cellulitis, abscess, neuropathic fracture, and deep venous thrombosis.[5]

Differential diagnosis of Charcot arthropathy and osteomyelitis: A significant proportion of patients with acute CN have a concomitant ulcer, further complicating the diagnosis, and raising the possibility of osteomyelitis. Moreover, the disease process may become reactivated by further trauma, making the differentiation from osteomyelitis more difficult.[14] Radiographs, largely useful for their anatomical information, may be normal or show only subtle changes at an early stage. Once established, bone and joint destruction, fragmentation and remodelling are evident. [15]Any associated osteomyelitis cannot be distinguished in the presence of severe bone and joint damage.[16] Early magnetic resonance imaging (MRI) appearances are non-specific, and can also be seen in bone-stressing phenomenon, acute osteomyelitis, reflex sympathetic dystrophy or sepsis. There is significant overlap of signal intensity from the marrow for infection and oedema. Established CN is characterised by a low T1 signal from the joint and a low T2 signal from the marrow.[16] Rapid onset CN with a high bone turnover rate and marked oedema is

associated with a high T2 signal, mimicking osteomyelitis.[17] (Figure 4)

Treatment

Goals of treatment are generally to avoid osseous prominences (which can lead to ulnceration) and to restore foot stability. Treatment of Charcot arthropathy is primarily non operative. Treatment consists of 2 phases: an acute phase and a post acute phase. Management of the acute phase includes immobilization and reduction of stress. Use of custom footwear in the post acute phase for foot protection and support is essential.[18, 19](Figure 5)

Immobilization: A total-contact cast is worn until the redness, swelling, and heat subside, generally 8 to 12 weeks, after which the patient should use removable braces or a Charcot restraint orthotic walker for a total of 4 to 6 months of treatment. The study conducted in Minneapolis showed that immobilization in a weight-bearing total contact cast appears to be a safe method of treatment of acute Eichenholtz Stage-I Charcot arthropathy of the foot and ankle. Twenty-seven patients with Charcot arthropathy of the foot and ankle were studied prospectively over a period of eighteen years, from 1988 to 2006. The average duration of follow-up was 5.5 years. Of the twenty-seven patients, twenty-six had diabetes mellitus. Total contact casts were used to treat thirty-four feet with Eichenholtz Stage-I or early Stage-II Charcot arthropathy. These patients were allowed to bear weight as tolerated. Casts were changed at weekly intervals and were worn until resolution of the acute stage of the disease.[20]

In on other study a custom, patellar-tendon bearing (PTB), patten-bottom, caliper suspension orthosis was constructed for six patients with severe, active (Eichenholtz stage I) Charcot arthropathy of the ankle and hindfoot. With the orthosis, the suspended foot and ankle remained completely non-weight-bearing, and the lower extremity supported full weight bearing along the posterior and anterior leg shells and PTB crest. Four of the six patients used the orthosis to ambulate without crutches, leaving the upper extremities free for functional use. Patient compliance was poor in four of the six patients. However, in the other two patients, the absence of mechanical forces on the foot and ankle in the orthosis allowed the swelling and erythema of the active phase of Charcot arthropathy to resolve within several weeks, with maintenance of functional ambulation during the months required for healing of the Charcot process.[21]

Bisphosphonates: There is as yet no pharmacological agent licensed for use in acute Charcot foot. A number of clinical trials assessing bisphosphonates in CN suggest clinical benefit. However, they are limited by the small number of participating patients. Bisphosphonates are synthetic analogues of inorganic pyrophosphate that decrease bone resorption by inhibiting the recruitment and activity of osteoclasts, while stimulating osteoblastic activity.[22] Bisphosphonates may shorten the lifespan of osteoclasts and provide pain relief through effects on prostaglandin E2 and other nociceptive substances. They have also been implicated to interfere with the release of neuropeptides and neuromodulators from afferent nerve endings.[23]

Pitocco et al. evaluated the oral efficacy of bisphosphonate compounds for the treatment of ACA patients during a 6-month randomized controlled trial. Their results showed a significant reduction in serum collagen COOH-terminal telopeptide of type 1 collagen and hydroxyprolin (known bone resorption markers) and noted clinical improvements in the Charcot foot at 6 months. Although some consider these studies as strong evidence supporting the use of bisphosphonates in the treatment of early-stage Charcot arthropathy , these drugs have not been approved by the US Food and Drug Administration for use in Charcot arthropathy patients.[24,25] In 1994, Selby et al. studied the effect of pamidronate on 6 patients with CN. These subjects received an initial infusion of 60mg followed by a 30mg infusion fortnightly over 12 weeks. Patients' symptoms and foot temperatures showed a significant improvement. Alkaline

phosphatase levels fell by about 25% by the end of the study.[26]

Calcitonin[27]: Secreted by the C-cells of the thyroid, calcitonin directly affects osteoclasts.

In a recent study, 32 patients were randomised to receive a combination of intranasal calcitonin (200IU/day) and calcium supplementation (100mg/day) or calcium supplementation alone. Disease activity improved in both groups but there was a significant reduction in bone turnover markers in the calcitonin treated group. In a follow-up study involving 36 acute CN subjects, [28] calcitonin treated patients had significantly faster healing compared to controls.[27, 29]

Surgery: is reserved for severe ankle and midfoot deformities that are susceptible to skin ulcerations and that make braces and orthotic devices difficult to use. Pinzur M. Compare Surgical treatment and accommodative treatment for Charcot arthropathy of the midfoot.[30] In this study during a 6-year period, 198 patients (201 feet) were treated for diabetes-associated Charcot foot arthropathy. At a minimum 1-year follow-up, 87 of the 147 feet with midfoot disease (59.2%) achieved the desired endpoint without surgical intervention. Sixty (40.8%) required surgery. Corrective osteotomy with or without arthrodesis was attempted in 42, while debridement or simple exostectomy was attempted in 18 feet. Three patients had initial amputation (one partial foot amputation, one Syme ankle disarticulation, and one transtibial amputation), and five had amputation (two Syme ankle disarticulations and three transtibial amputations) after attempted salvage failed. Therefore he conclude that with using a simple treatment protocol with the desired endpoint being long-term management with commercially available, therapeutic footwear and custom foot orthoses, more than half of patients with Charcot arthropathy at the midfoot level can be successfully managed without surgery.

Effect of pro-inflammatory cytokines in acute Charcot: one study showed that increased bone turnover in acute Charcot is associated with increased concentrations of pro-inflammatory cytokines, related signalling peptides and bone turnover markers.[31] 17 patients newly presenting with acute Charcot in diabetes and 16 non-diabetic patients without neuropathy undergoing elective forefoot surgery provided informed consented to participate. Samples of bone were taken by needle biopsy, and were stained with H&E to determine bone architecture and bone remodelling. They found that classic histopathology features of fracture and bone remodelling were evident in Charcot bone biopsies. Systemic circulating concentrations in the Charcot group antecubital vein for both I6 and OPG were significantly greater than in controls ($p<0.05$). There were no significant differences between the dorsal vein concentrations of any analyte when the affected and unaffected feet were compared. Therefore the elevation in CTX observed in the affected foot in patients with an acute Charcot foot reflects the bone breakdown and remodelling which is present. The higher circulating concentration of IL-6 in the Charcot patient group, reflects the inflammation which is present and which is thought to be central to the development of the condition.[31]

Osteoclastic activity and bone resorption in Charcot arthropathy[32]: An immunehistochemical study into destruction of bone architecture from Charcot arthropathy in the foot found it was related to enhanced bone resorption and increased osteoclastic activity. Results suggest it may eventually be possible to use pharmacologic agents to treat this condition and control its destructive effects. Researchers used 20 specimens that were fixed in formalin, decalcified, placed in paraffin blocks and sectioned. H&E staining was done with additional immunohistological staining in nine of the specimens for polyclonal antibodies for IL-1, IL-6 and TNF. Rheumatoid arthritis antibodies known from previous studies to express the same cytokine mediators were used. Positive controls were inflammatory cells from rheumatoid synovium tissue sections. A majority of specimens were from patients

(average age 55) with type 2 diabetes and Eichenholz staging grade 2. Most were from men. Five specimens had noninfected ulcers. They observed increased number of osteoclasts, increased cell mediators for bone resorption — IL-1, IL-6, and TNF — which led to increased osteoclast differentiation, proliferation and recruitment

Table 1: Charcot arthropathy anatomical classification

Pattern	Location	Description
I	Forefoot	Involving the interphalangeal joints, phalanges, metatarsophalangeal joints, and/or distal metatarsal bones; commonly occurring pattern, also seen with plantar ulceration; seen as osteopenia, osteolysis, juxtaarticular cortical bone defects, subluxation, and destruction on radiographs
II	Tarsometatarsal joints	Involving the tarsometatarsal joints and metatarsal bases, cuneiforms, and cuboid; commonly occurring pattern, with greater frequency in diabetic patients than in patients with leprosy; may be associated with plantar ulceration at the apex of deformity; seen as subluxation or fracture–dislocation, collapse of midfoot, and resultant rocker-bottom foot deformity (consistent with initial features of osteoarthritis) on radiographs; may have dorsal prominence at metatarsal bases; late changes include fragmentation
III	Naviculocuneiform, talonavicular, and calcaneocuboid joints	Involving usually the naviculocuneiform joint and navicular bone but also the other midtarsal joints and bones; ulceration may occur at the apex of deformity and may be in combination with Pattern II; on radiographs, seen as osteolysis of naviculocuneiform joints with fragmentation; with osseous debris both dorsally and plantarly
IV	Ankle and subtalar joints	Involving the ankle joint with or without the subtalar joint and medial or lateral malleolar fracture; considered a severe structural deformity with instability—may even be associated with minor ankle sprain; on radiographs, seen as malleolar fractures, erosion of bone and cartilage with collapse of joint, free bodies in ankle, extensive destruction, and lateral dislocation of ankle
V	Calcaneus	Rarely involving only the calcaneus bone and usually involving an avulsion fracture of the posterior tubercle; although no joint is involved, the pattern develops in patients with Charcot arthropathy; on radiographs, seen as osteolytic changes in the posterior calcaneus attachment of the Achilles tendon; avulsion fracture of the posterior tubercle may ensue; osteolytic changes may also occur at the naviculocuneiform joint due to additional stress during liftoff in the gait cycle (this may be due to lack of an Achilles tendon attachment to the calcaneus)

Table 2: Modified Eichenholtz stages

Stage	Phase	Description
0	Inflammatory	Localized warmth, swelling, and redness; minimal to no radiographic abnormalities; MRI may show nondisplaced pathologic fracture(s) and increased marrow edema to the foot and/or ankle
1	Development	Localized warmth, marked swelling, and redness; radiographic presence of bony debris, fragmentation of subchondral bone, periarticular fracture, subluxation, and/or dislocation
2	Coalescence	Continued but decreased warmth, swelling, and redness; radiographic presence of absorption of fine debris, new bone formation, coalescence of fragments, fusion of joints (ankylosis), and/or sclerosis of bone ends
3	Remodeling	Marked decrease or absence of warmth, swelling, and redness; physically enlarged fixed ("healing") deformity; radiographic appearance of remodeled and new bone formation, decreased sclerosis, and/or possible gross residual deformity

Figure 1: Foot deformity characteristic of established Charcot foot

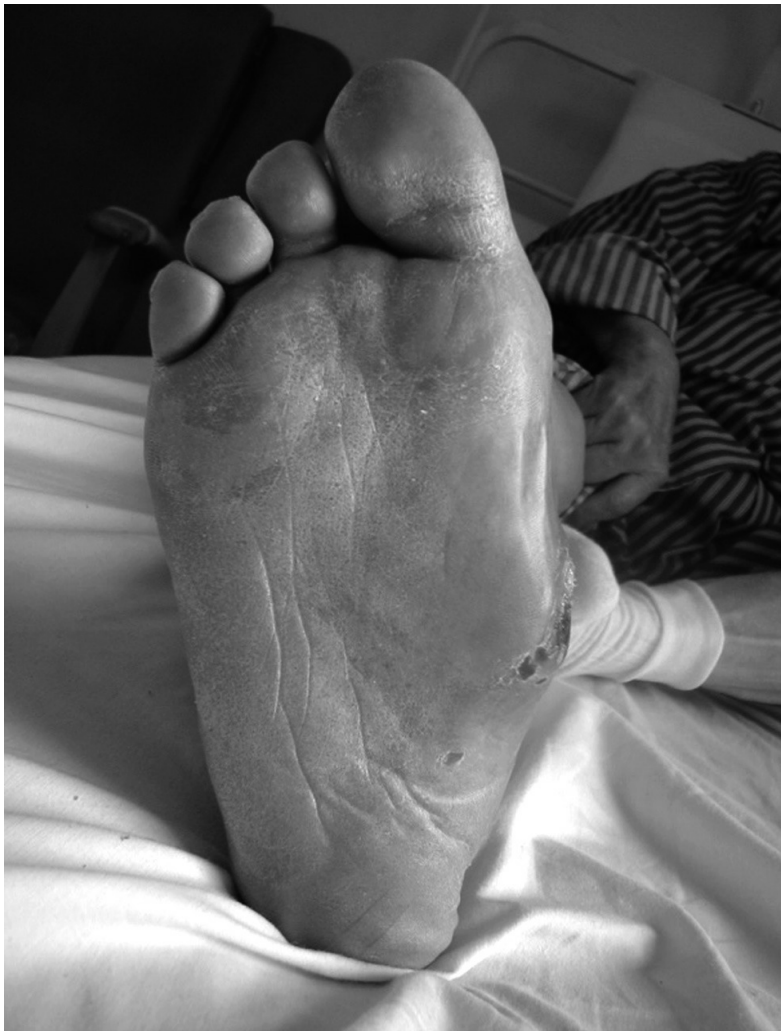


Figure 2: Foot deformity characteristic of Charcot neuroarthropathy

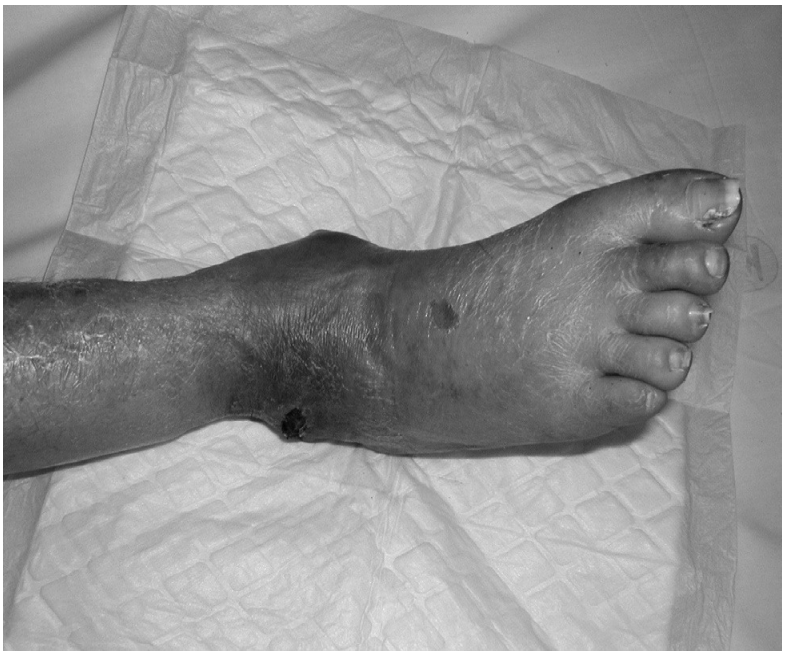


Figure 3: Ethiology of charcot

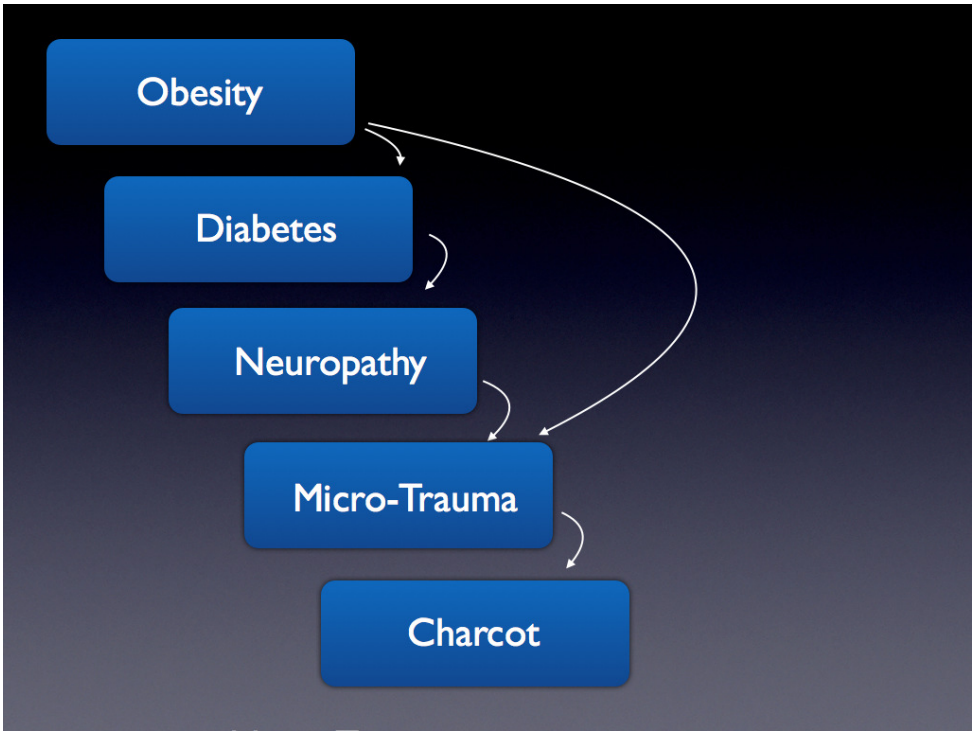


Figure 4: An algorithm depicting the basic approach to the Charcot foot and its differentiate diagnosis

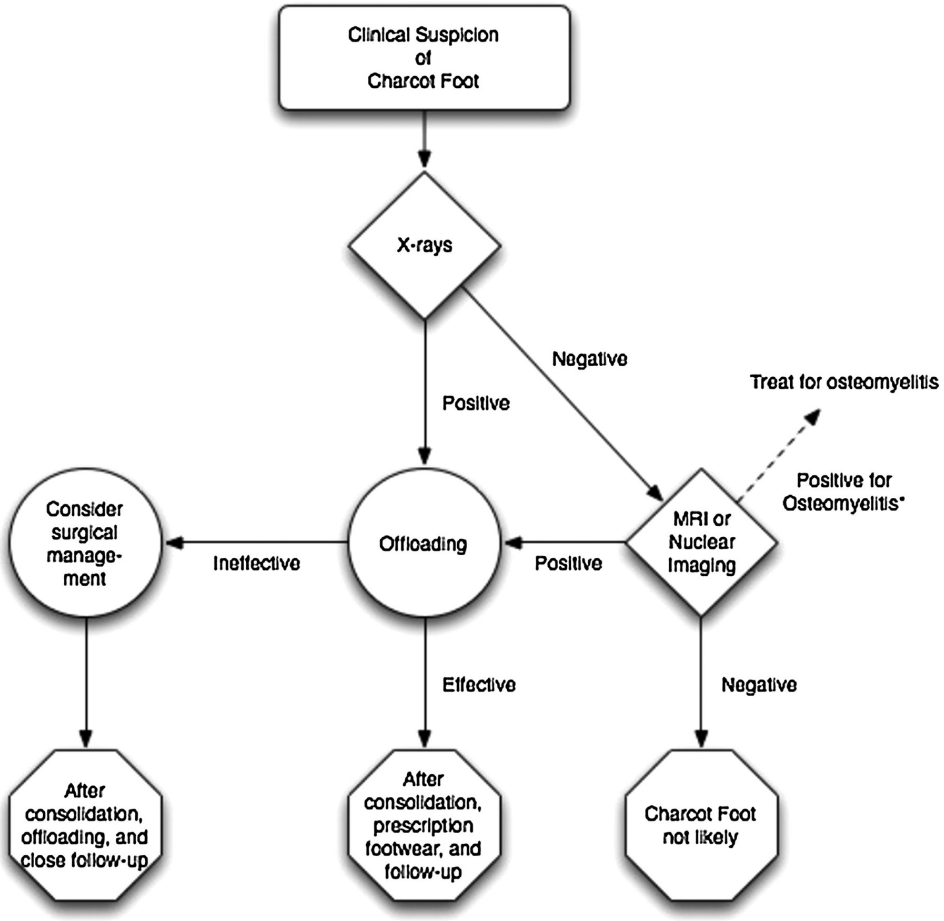
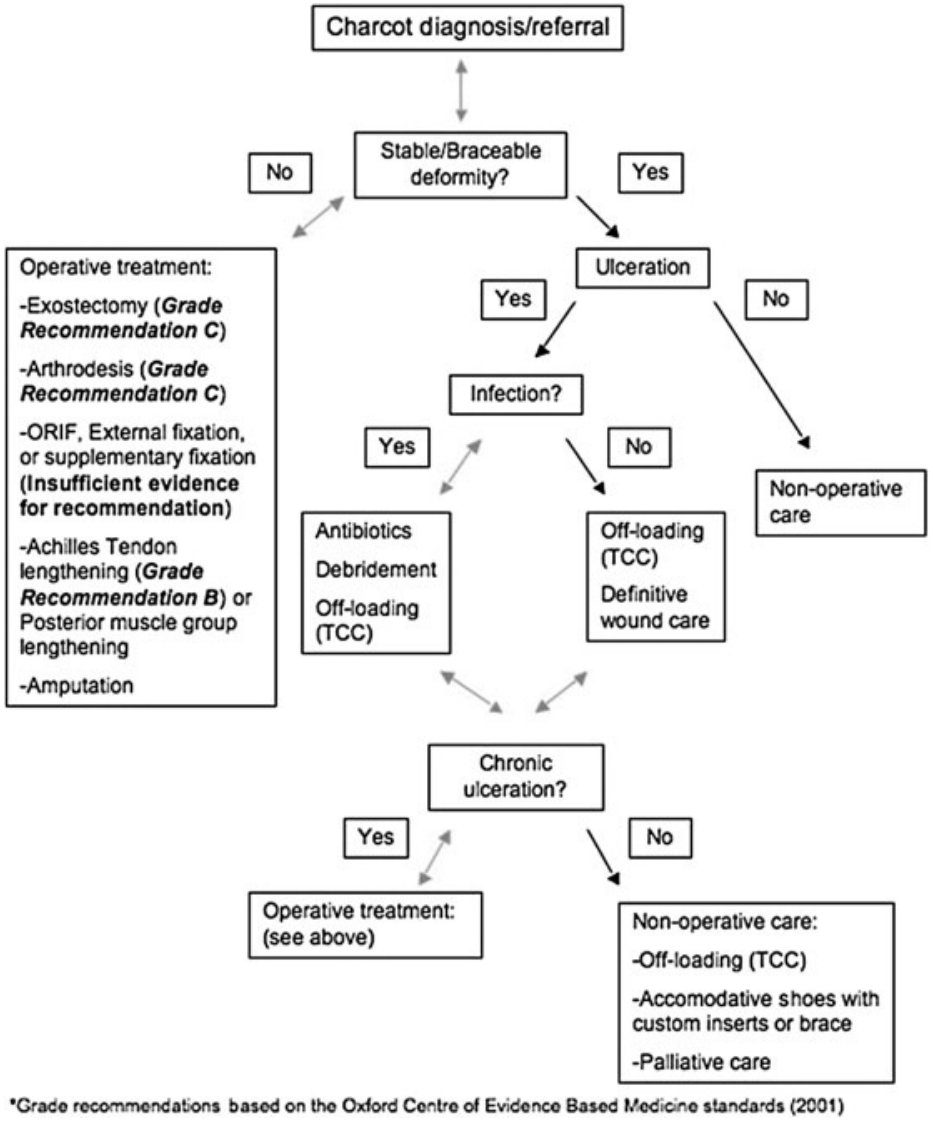


Figure 5: Charcot arthropathy treatment algorithm



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