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SYMPOSIUM

Utilization of Advanced Modalities in the Management of Diabetic Charcot Neuroarthropathy

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Abstract

Technological advances have allowed reconstructive foot and ankle surgeons greater opportunity to provide significant limb salvage options to those patients who present with significant lower extremity deformity due to diabetic Charcot neuroarthropathy. Paradigms that promote the utilization of these advanced modalities have demonstrated significant improved limb salvage outcomes in this challenging patient population and have consequently improved the quality of life for patients. The purpose of this review is to discuss current concepts in Charcot reconstruction.

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Introduction

Charcot neuroarthropathy (CN) is a debilitating condition typically affecting diabetes patients with peripheral neuropathy. Severe foot and ankle deformity, recalcitrant ulcerations, and subsequent amputations have resulted from untreated, improperly diagnosed CN. Early morphological diagnosis and progression of the disease are critical to proper treatment and management. Many new advances in diagnosis, initial treatment, surgical intervention, and surgical bioadjuvants are promising for the prevention of disease progression. There are many new advances in CN such as orthobiologic agents as well as advanced surgical approaches to address the complex Charcot patient. This article aims to address the new concepts, surgical as well as nonsurgical, in treating these difficult patients.

Etiology

Although research for CN is ample, pathogenesis is still uncertain. There are two well-recognized theories—the neurotraumatic theory and the neurovascular theory—that are widely accepted today. The neurotraumatic theory was initially theorized by Jean-Martin Charcot in 1868. This theory suggests that an insensate joint is exposed to extensive microtrauma leading to typical Charcot changes.[1] This abnormal sensation inhibits the individual from utilizing protective sensation or daily activity modification. The neurovascular theory implies an abnormal increase in circulation to the affected limb by arteriovenous shunting, ultimately resulting in bone remodeling, resorption and weakening.[2]

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Abbreviations: (BMP) bone morphogenetic protein, (CN) Charcot neuroarthropathy, (CROW) Charcot restraint orthotic walker, (OP) osteogenic protein, (PRP) platelet-rich plasma, (TCC) total contact cast

Keywords: axial screw fixation, bone stimulation, bioadjuvants, Charcot neuropathy, Charcot restraint orthotic walker, total contact cast

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Nonenzymatic glycosylation of proteins due to a hyperglycemic state leads to changes in tissue morphology of both bone and soft tissue.[2] Equinus, whether the initial deforming force or a subsequent finding from disease progression, is often a clinical finding.

Presentation

Typical presentation of CN is often associated with advanced complication of diabetes mellitus; however, the disease was initially associated with long-standing syphilis. Associated conditions include alcoholism, leprosy, tabes dorsalis, myelomeningocele, and congenital insensitivity to pain.[3] Charcot neuroarthropathy patients typically present with a warm, edematous, and erythematous foot and ankle almost entirely indistinguishable from infection. Distal pedal pulses are a notable characteristic in this disease progression. Leriche and Fontaine[4] in 1927 felt autonomic denervation lead to a hyperemic state, some speculating the cause of this state of dependent rubor. Historically, misdiagnoses range from gout, arthritis, fracture, venous insufficiency, tumors, to infection.[5] One simple diagnostic test that can be performed in the office is to elevate the affected extremity. Distinguishing dependent rubor of CN from cellulitis can be evaluated by simply raising the leg in some cases.[6] In this example, raising the leg in a patient with dependent rubor will cause rubor to subside, whereas cellulitis will remain. Patients with CN have arteriovenous shunting, which can cause rubor much like a patient with peripheral arterial disease. Patients with acute CN should also be evaluated for skin temperature differences between the lower extremities. The measurements should be taken from the area of maximal deformity and the corresponding site on the contralateral limb. Any temperature difference greater than 2 °C using an infrared thermometer should be considered high risk for acute CN.[7] Staging of CN has also become a valuable step for determining appropriate treatment. Eichenholtz[8] comprised a radiographic classification system for the progression of CN in 1966, which was later modified by Shibata and colleagues in 1990.[5] Stage 0 involves normal radiographic findings but a loss of progressive sensation with swelling and erythema. Stage 1, or the fragmentation stage, is notable for osteopenia, periarticular fragmentation, fracture, and/or subluxation. Stage 2, or the coalescence stage, involves the absorption of debris, early signs of fusion, and sclerosis. Lastly, stage 3, or the remodeling stage, is notable for joint arthrosis, osteophytes, and subchondral sclerosis.[8]

Diagnostic Imaging

On initial presentation, CN is often difficult to assess from infection. Radiographs have only been shown to have 50% specificity for detecting osteomyelitis; however, it is an essential first step for evaluating the CN versus bone infection (**Figure 1**).[9] Currently, there is no definitive imaging modality to discern osteomyelitis from CN. When evaluating suspected CN versus osteomyelitis, the best alternative is a three-phase technetium Tc-99m methylene diphosphonate scintigraphy followed by indium In111-labeled leukocyte scintigraphy.[4] This current imaging technique has been proven to have between 93% and 100% sensitivity and specificity of approximately 80%.[10,11] Although there can be false positives with the indium scan, the combination with the technetium scan in addition to the indium scan yields a more accurate scan for the diagnosis of CN. In addition to diagnostic properties, bone scanning can be useful for assessment of bone turnover and disease progression and activity monitoring in CN.[12] In addition, bone mineral testing by duel-energy X-ray absorptiometry has been shown to be significantly lower in affected lower extremities of CN patients.[13]

Nonoperative Therapy and Medical Management

Immobilization is the key initial intervention in the acute stages 0–1 CN patient. Numerous widely used modalities are available to accomplish the goal of immobilization of the affected and oftentimes unaffected limb. The total

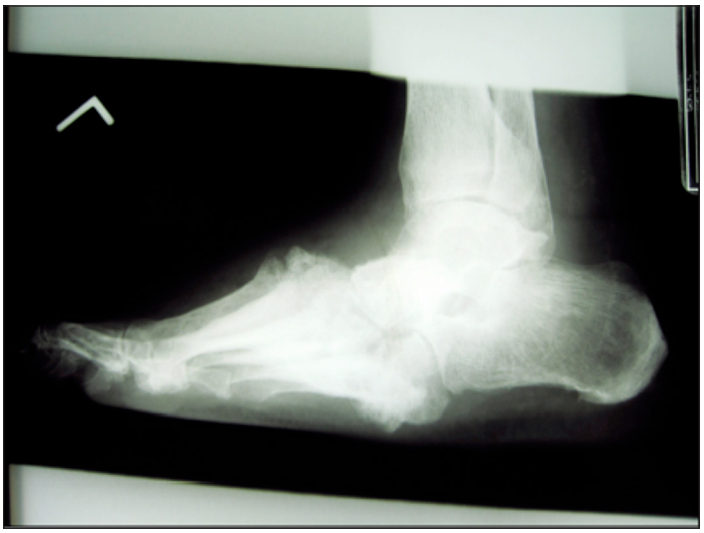

Figure 1. Charcot neuropathy with cortical disruption and collapse of the midfoot, which can commonly be misdiagnosed as osteomyelitis.

contact cast (TCC) is a widely used and acceptable initial treatment option.[14] The TCC is applied for two weeks at a time and should be changed appropriately to accommodate for edema. Non-weight bearing and offloading should be maintained for at least 8–12 weeks or until progression to stage 2 or coalescence is noted.[5] In the high-risk population, 72% contralateral fracture of limb has been theorized. In contrast to immobilization of the contralateral limb, some physicians find it acceptable to allow weight bearing on an immobilized limb.[15] Once progression to stage 2 is noted, a Charcot restraint orthotic walker (CROW) or similar type orthotic can be allowed for continued immobilization. The CROW is a custom bivalve total contact ankle foot orthosis that is lined with various foams of different densities housed in a rigid polymer shell (**Figure 2**).[16]

In adjunct to immobilization, the use of bisphosphonates has been theorized in stages 0–1 of CN. In one study, pamidronate showed a decrease in acute activity of CN by measure of decrease in skin temperature as well as measuring plasma and urinary bone turnover markers.[17] The mechanism is centered around osteoclastic inhibition and osteoclast apoptosis.[18] New research on intranasal calcitonin has also lead to promising reduction in bone turnover in studies.[19]

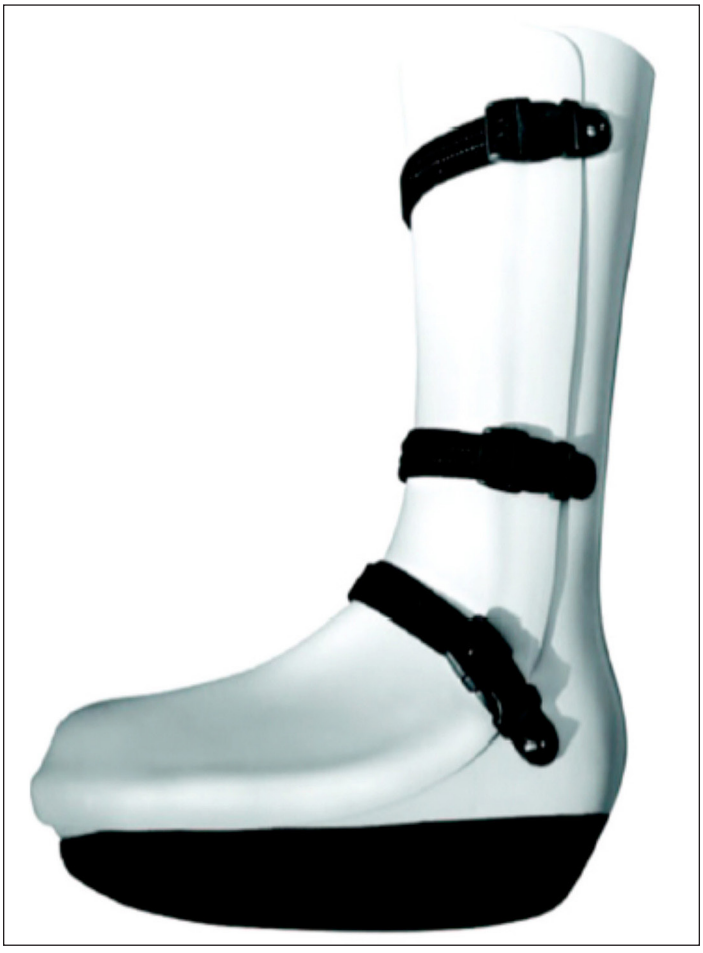

Figure 2. The CROW walker is a custom bivalve total contact ankle foot orthosis that is lined with various foams of different densities housed in a rigid polymer shell, that distributes pressure in the affected extremity, and that can limit further osseous breakdown.

Current Concepts in Surgical Management

Current operative management of CN has become an area of increasing debate in the literature. One concept, however, can be universally accepted: the chosen surgical procedure should result in a stable, plantigrade foot. Classic CN presentation is the collapse and destruction of the midfoot, although around 5% CN affects the ankle joint.[20] Typical fixation methods have proven futile due to poor bone quality, poor vascularity, and impaired nutrition of glycosylated tissue in diabetes patients and have thus failed postoperatively.[21] Careful dissection is of utmost importance in these procedures as well as anatomy of the soft tissue can be markedly disturbed. Oftentimes, tendons remain attached to their respective attachment sites but become quite mobilized due to the progression of CN.[16] Simple exostectomy of bony prominences are often discussed but are only acceptable in the stable Charcot foot. Advancements in plantar plating, axial screw fixation, locked plating, retrograde nailing, and external fixation have alerted surgeons on ways to circumvent these fixation issues.

Preoperative management is of utmost importance in the CN patient. Medical comorbidities should be evaluated as well as age and nutritional status. Preoperative renal and cardiovascular assessment should be performed by the appropriate teams. Transcutaneous oximetry should be performed preoperatively as well. A pressure gradient of >30 mm Hg is an acceptable preoperative assessment.

Plantar plating is a fixation method that is most pertinent for fixation with Charcot involving midfoot collapse. Plantar plating allows for fixation to extend past the area of involved bone into the area of uninvolved dense bone (**Figure 3**).[21] Locked plating techniques have the specific advantage of improving fixation in bone of poor stock. The plantar plate construct cannot be placed across the talonavicular joint, as the sustentaculum tali tends to be insulated with this technique.

For CN reconstructions to succeed, four important surgical techniques are being employed. First, in order to obtain successful arthrodesis, the intended site for fusion must extend beyond the zone of injury and include

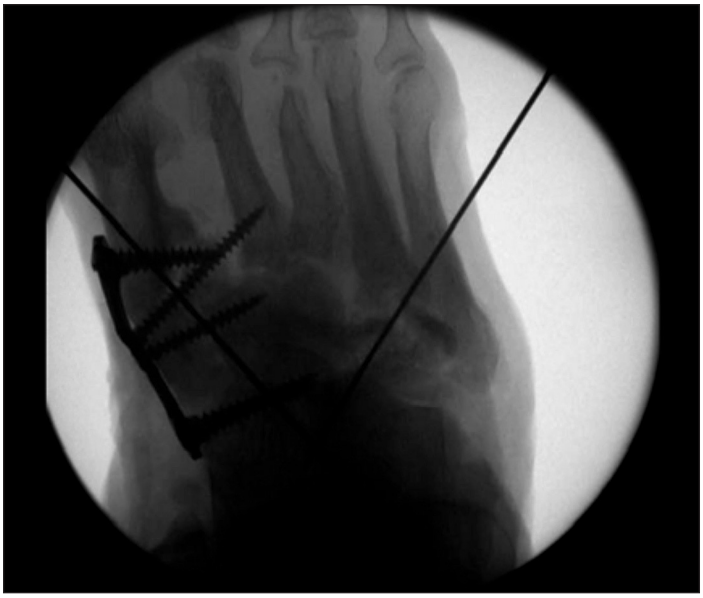

Figure 3. Plantar plating allows for fixation to extend past the area of involved bone into an area of uninvolved dense bone.

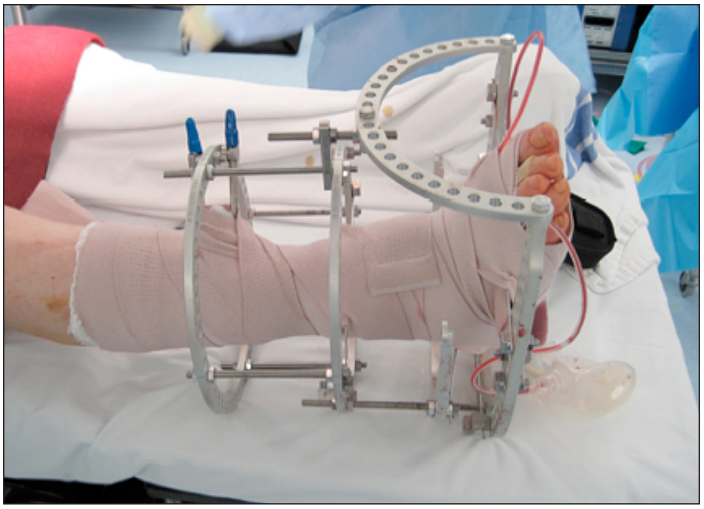

Figure 4. Hybrid external fixation devices can be utilized to provide spanning stabilization across lower extremity reconstructive constructs.

nonaffected bone and joint surfaces. Second, bone resection shortens the extremity to allow for decreased tension on the soft tissue envelope surrounding the affected area. Third, the strongest form of fixation must be employed that can be tolerated by the soft tissue in question. Lastly, the hardware must be applied in a position applying maximal mechanical function.[21] Commonly, external fixation is utilized to provide spanning stabilization constructs to provide significant stabilization following lower extremity reconstruction in patients with CN (**Figure 4**).[22]

Axial screw fixation for midfoot reconstruction entails passing either a retrograde or antegrade screw into the intramedullary canal of the metatarsals. Stress risers of already weak cortical bone are eliminated in this technique.[21] Fusion can be continued proximally by denuding all cartilage of the respective metatarsal cuneiform joint as well as the naviculo-cuneiform joints and the talonavicular joint.[16]

Although CN affects the ankle and rearfoot much less frequently, the resultant deformity leads to a deformity that is much more limb threatening where amputation may be inevitable without intervention. One method of fixation is the retrograde nail for either tibiocalcaneal arthrodesis or tibiotalar arthrodesis. Again, this procedure allows for a reasonably high fusion rate without requiring purchase of poor-quality bone stock.[22]

Achilles tendon contracture is often present in CN and must be addressed. Contracture at the Achilles tendon places increased stresses at the midfoot, rearfoot, and ankle joint. The equinus deformity must be addressed to realign the calcaneal inclination angle. Many different lengthening procedures have been proposed. Percutaneous tendo-Achilles lengthening procedures have been performed, but a 10% rupture rate has been reported.[23] Open Achilles tendon lengthening via *z* lengthening is another recognized procedure. This technique involves direct visualization of the tendon and lower post-operative risk for rupture.

Bioadjuvants for Charcot Reconstruction

Complex surgical reconstruction of CN is not without a high complication rate. Diabetes significantly increases incidence of nonunion, delayed union, and pseudarthrosis. In order to decrease devastating consequences, bioadjuvants and orthobiologic agents can be implicated to accelerate the healing process.[24] Advances in orthobiologic agents include platelet-rich plasma (PRP), bone morphogenic proteins, and demineralized bone matrix among others.

The healing process progresses through a predictable three-stage process: (1) inflammation, (2) proliferation, and (3) remodeling. Platelets play a critical role in the inflammatory phase. Platelets, white blood cells, and red blood cells form a clot at a trauma location regardless of type. Platelet circulation time is approximately 10 days. Following injury, platelets release several important growth factors involved in bone healing: transforming growth factor-β, insulin-like growth factor, and platelet-derived growth factor.[25] Platelet-derived growth factor stimulates mesenchymal cell proliferation and osteocyte generation.[24] Platelet-derived growth factor also enhances

differentiation of osteoprogenitor cells toward an osteoblastic lineage.[26] Transforming growth factor-β is responsible for proliferation and expression of chondrocytes and osteocytes and promotion of angiogenesis.[24] Insulin-like growth factor is responsible for stimulating osteoblastic cell line proliferation during cell maturation.[27] Producing an increased level of these three critical growth factors can be accomplished by induction of PRP to the area of trauma itself, in this case, the area of Charcot reconstruction. Platelet-rich plasma is obtained from autologous blood, which is typically a platelet concentration five-fold increase above physiologic levels.[28] Pinzur[29] reported a 91.3% fusion rate with high-risk Charcot reconstruction patients in 2009 using PRP injections at the conclusion of his procedures. In this study, patients were high-risk patients for nonunion due to presence of infection, multiple comorbidities, and extreme body habitus, and excellent fusion rate was noted.

The formation of bone is contingent upon osteogenesis, osteoinduction, and osteoconduction. Osteogenesis is the ability of cells, once implanted, to form bone utilizing osteoblastic stem cells and progenitor cells. Osteoinductivity is the ability to alter the differentiation of stem cells and progenitor cells along an osteoblastic pathway. Lastly, osteoconductivity is the ability to provide a scaffold for new bone to be laid upon (**Figure 5**).[28] Bone morphogenic proteins are osteoinductive proteins much like cancellous bone. Bone morphogenic proteins are important mediators of these pathways. Bone morphogenetic proteins (BMPs) promote cellular proliferation, apoptosis, differentiation, and morphogenesis.[28] BMPs were first observed by Marshall Urist with *de novo* bone formation in rats after implantation.[30] Currently, there are over 20 identified BMPs; BMP-2, BMP-4, and BMP-7 have been found to have the most significant role in bone formation, and commercially available specimens contain BMP-2 and BMP-7.[31] In 2000, osteogenic protein (OP)-1 (BMP-7) was approved for nonunion of long bones.[28] BMPs have long been used for spinal fusions as adjuncts or substitutes for bone grafting. In 2009, Schuberth and associates[32] reported OP-1 was used in complex Charcot reconstructions as well as many other complex foot and ankle reconstructive procedures, with an overall 84.21% fusion rate. It has since been used for rearfoot and ankle fusions with good success as well.[33]

In addition to orthobiologic agents, bone stimulation devices have come into favor to facilitate challenging CN cases. There are currently three distinct types of bone stimulation devices available: direct current, capacitive coupling, and pulsed electromagnetic field.

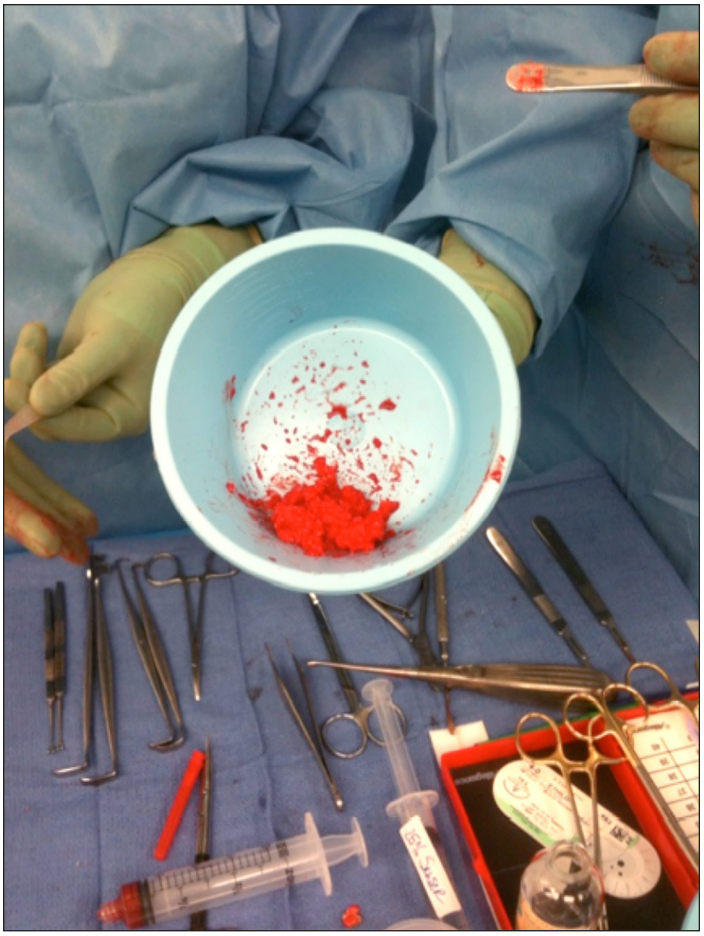

Figure 5. Platelet-rich plasma mixed with bone marrow aspirate and an osteoconductive matrix can be utilized to provide both osteoinductive and osteoconductive functionality to promote increased bone healing at fragile arthrodesis sites.

Direct current devices are implantable devices that have either a single or double titanium cathode electrode that can be placed directly into the desired site. The battery unit incorporates the anode and is typically placed subcutaneously.[28] Direct current devices often involve a secondary procedure for removal of device, can cause irritation, and can cause an area of prominent hardware. The benefit of this device is the lack of difficulty with patient compliance. Capacitive coupling devices place the electrodes percutaneously over the area of interest. Disadvantages to the system include the requirement of 3–10 hours of use per day; therefore, patient compliance can be an issue. Pulsed electromagnetic field uses local pulses of electricity on the area of interest in the form of electromagnetic field. The device can be applied directly to the skin or a cast. Daily usage requirements are 3–10 hours, thus patient compliance is again an issue.[28] *In vitro* studies have shown that pulsed electromagnetic field devices promote healing through differentiation of fibrocartilage cells.[34] Direct current devices promote

healing through an increase in intracellular free calcium and hydrogen peroxide and over increase in pH at the desired site.[35] Capacitive coupling devices increase osteoblastic proliferation.[36] Currently, sufficient data do not support implanted versus nonimplanted devices.[37] Hockenbury and coworkers[38] had a particularly difficult group of patients with an unstable, infected CN who underwent Charcot reconstructive procedures as well as implantable direct current bone stimulation with successful outcomes.

Demineralized bone matrix is both an osteoinductive and osteoconductive bone graft substitute that is derived from cortical bone.[39] Demineralized bone matrix is available in a variety of forms, which makes for excellent augmentation to many types of surgical procedures. Demineralized bone matrix is currently available in gel, putty, paste, powder, chips, granules, and various other forms.

Conclusion

Advancements in technology have greatly increased the reconstructive foot and ankle surgeons' armamentarium for the management of complex lower extremity deformity due to CN. These advances, such as improved internal and external fixation techniques, have allowed for improved surgical outcomes with maintenance of a plantigrade, shoe-able foot. Additionally, the development of bio-adjuvants orthobiologics have improved the bone- and wound-healing outcomes in this classically challenging patient population. These advanced technologies have significantly improved the limb salvage options available to the lower extremity reconstructive surgeon, and paradigms that advocate the usage of such advanced modalities have demonstrated significant improvement in limb preservation rates as compared to previous techniques.

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