Current Concepts

Charcot Neuroarthropathy: Current Concepts

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In orthopaedics, there are exceptionally few disease entities that are as poorly understood and devoid of evidence-based guidelines as there are with Charcot Neuroarthropathy (CN) of the lower extremity. CN is associated with high morbidity and mortality rates, with its financial impact on the healthcare system being substantial. The disease is likely due to the combination of the previously described neurovascular and neurotraumatic theories. Thus, physicians should highly suspect CN in any diabetic patient with ulcers or apparent deformities. The recognition and further classification of CN can then help guide further management, which includes both nonoperative and operative approaches. The optimal timing for surgical intervention remains unknown; however, some authors have successfully operated during the acute phase of the disease. Caring for the Charcot patient requires a multidisciplinary approach, including infectious disease specialists, endocrinologists, wound care teams, social workers, and surgeons. As there are no current widely accepted evidence-based guidelines or algorithms used to manage patients, our topical review provides a framework for understanding, diagnosing, staging, and managing a patient with CN in addition to the author's preferred treatment method and our approach to a patient diagnosed with CN.

INTRODUCTION

In the realm of orthopaedic surgery, there are exceptionally few disease entities that are as poorly understood and devoid of evidence-based guidelines as there are with Charcot Neuroarthropathy (CN). Yet, the socioeconomic impact of the disease continues to be a tremendous cost to our healthcare system with minimal change in morbidity or mortality.[1,2]

As the rate of diabetic neuropathy increases, so will CN. A greater effort must be placed on understanding this disease and formulating treatment guidelines. Fortunately, over the last decade, there has been a steady increase in basic science research aimed at understanding the pathophysiology of this disease, and recently, our lab has published the first animal model that mimics the neurodegenerative human Charcot condition.[3-5] Furthermore, several new surgical techniques and adjuvants have emerged in the surgical treatment for CN.[6-8]

While there is still a paucity of literature from which to form evidence-based practice guidelines, a summary of the most current knowledge will be beneficial in guiding future research in the hope of developing best practices for clinicians treating this disease. As such, the following topical review will highlight advances in the treatment and understanding of CN.

REVIEW

BACKGROUND & PATHOPHYSIOLOGY

CN of the lower extremity is a progressive, neurodegenerative disease that arises from the combination of peripheral neuropathy and trauma. CN can destroy foot anatomy, resulting in ulcers, infection, and even amputation.[3] While the true prevalence of CN is unknown, estimates range from 0.1% to 10% among patients with diabetes. These values increase to 35% among patients with diabetes and peripheral neuropathy.[9]

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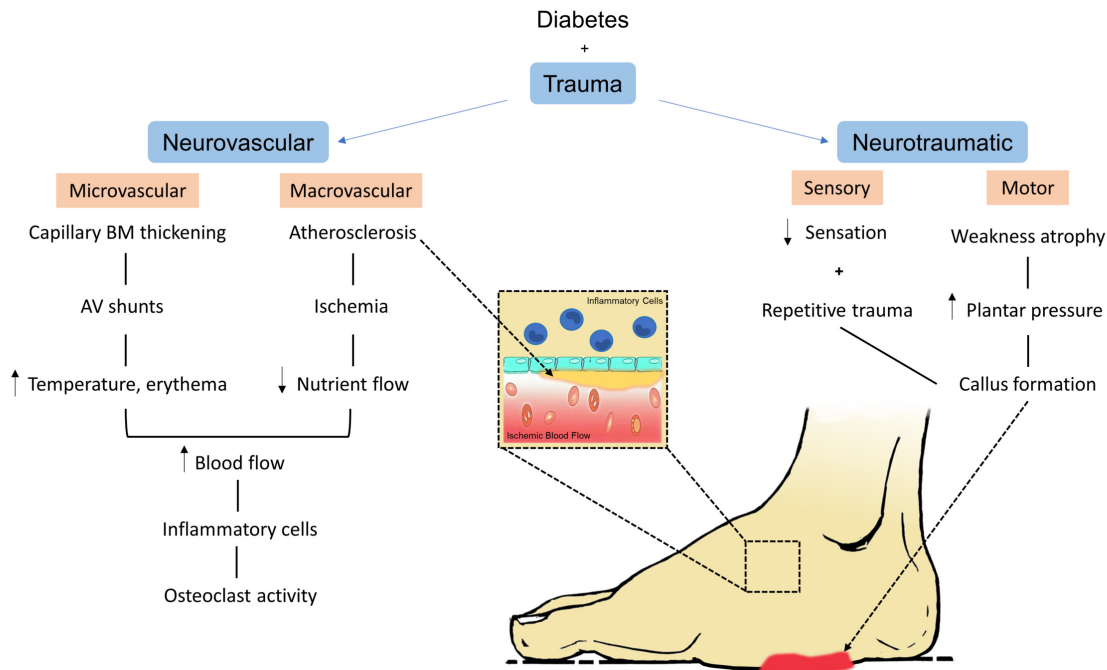 kdopke@pennstatehealth.psu.edu

Figure 1. Pathophysiology of Charcot neuroarthropathy and patient presentation with radiographs.

Two theories, neurotraumatic and neurovascular, are proposed in CN. The neurotraumatic theory involves decreased sensation and repetitive trauma, leading to callus formation. The neurovascular theory is characterized by ischemia and damage to surrounding tissues. Increased blood flow leads to increased inflammatory cell migration and osteoclast activation.

CN is associated with high rates of morbidity and mortality. For example, a retrospective study evaluating outcomes of 173 CN patients found a mean survival of 12.7 years after the first diagnosis and a 14% 5-year mortality rate.[10] This same study determined the complication frequency to be 63%, with 10% of patients requiring a major amputation.[10] Furthermore, in patients that go on to require amputation, research has estimated 5-year mortality up to 55% and 74%.[11,12]

The leading hypothesis of the pathophysiology is developed around a neurovascular and neurotraumatic theory [**Figure 1**]. Peripheral neuropathy, abnormal neuropeptide release, trauma, and abnormalities in the microvasculature of the leg have been shown to increase blood flow, leading to a rise in venous pressure and subsequent enhanced capillary leak.[13,14] This raises compartment pressure, which causes arteriovenous shunting and local ischemia, damaging the surrounding ligaments and joints.[13,14]

In addition, the repetitive acute and subacute trauma occurring secondarily to the loss of peripheral sensation initiates a reaction mediated by several proinflammatory cytokines. These cytokines promote excessive osteoclastogenesis and bone turnover by upregulating the receptor activator of nuclear factor-κB (RANK) and the receptor activator of nuclear factor-κB ligand (RANK-L). Moreover, repetitive trauma reduces anti-inflammatory cytokines, further perpetuating this cycle. This theory has been supported by several studies that have reported elevated levels of TNF-alpha, IL-6, and C-reactive protein in patients with CN.[13,15]

The current neurovascular and neurotraumatic theory has been supported by King *et al.*, who developed a novel FEMASK-scoring system based on histopathological findings of CN.[4] The FEMASK-scoring system uses a scale of 0,1,2,3, indicating distinctive intraneural arteriolosclerosis, the first stage of CN with large, embedded bone or cartilage fragments, the second stage showing mixed large and small bone fragments, and the end stage with complete absence or resorption of bone fragments, respectively. Their reproducible results demonstrate the pathogenesis of CN, and the scoring system will help surgeons determine adequate treatment that can be correlated to patient outcomes.

Apart from neurovascular and neurotraumatic theories, genetics may influence CN development.[16] Mitchell *et al.* found fewer synovial mesenchymal stromal/stem cells in patients with CN than without. Pasquier *et al.* noted an altered expression profile of circulating miRNAs, and Guo *et al.* suggested that calcitonin gene-related peptide (CGRP) may also play an important role due to its ability to stimulate collagen degradation in vivo because higher rates of CGRP in the synovium of patients with CN were discovered.[17-19] Lastly, there are alternative causes of Charcot other than diabetes, such as syphilis, alcoholism, B12 deficiency, and idiopathic.

PRESENTATION AND WORKUP

Early diagnosis of CN is difficult due to varied symptoms. However, any patient presenting with diabetic neuropathy and lower extremity swelling, pain, edema, redness, or deformity should be considered.[3] Patients with CN who present acutely will have a temperature difference of at least

2°C compared to the contralateral unaffected side, and elevating the limb will resolve the redness and can easily differentiate CN from infection.[3,9] Short *et al.* described that early and accurate imaging and a thorough history and physical exam are crucial for differentiating CN from osteomyelitis.[20] Patients may present with severe foot deformities in the later stages due to metatarsal collapse and joint destruction. The loss of the medial longitudinal arch may cause the classic "rocker-bottom" deformity.[21]

For suspected CN, standard, weight-bearing, orthogonal radiographs of the foot and ankle with contralateral comparison views are essential to diagnose subtle and early collapse and to monitor progress, albeit radiographs may be normal during the early stage of the disease. Likewise, Magnetic Resonance Imaging (MRI) or computerized tomography (CT) scans for patients with contraindications can be ordered using a large field view to help confirm the disease, monitor progression, and evaluate response to treatment.[22,23] However, MRI is limited in its ability to distinguish active CN from acute osteomyelitis.[24] A recent meta-analysis concluded that while MRI, white-blood-cell scintigraphy, and positron emission tomography (PET) scans all have similar sensitivies for detecting osteomyelitis, PET scans have an overall higher specificity.[25]

While many physicians routinely obtain inflammatory markers, such as C-reactive protein (C-RP) erythrocyte sedimentation rate (ESR), these have little value in the diagnosis of CN due to their nonspecific nature. No specific biomarker has been identified for diagnostic purposes. Hemoglobin A1c (HbA1c) is a good indicator of glycemic control and should be obtained in diabetic patients, while vitamin B12 should be ordered for non-diabetic patients.[26]

After diagnosis, the Eihenholtz, Brodsky, or Sander-Frykberg classification may be used to guide treatment.[27] At our institution, we have employed a combined approach utilizing the Eichenholtz staging combined with pathologic grading. This combined approach demonstrates strong correlations with predicting outcomes defined as preventing the progression of the disease and salvage amputations in Charcot patients.[4] In addition, some consensus groups recommend using "active" and inactive" Charcot to clinically stage.[28] Regardless of the classification system used, research has suggested all three can still be useful in helping with the diagnosis and management of CN.[27]

NONOPERATIVE TREATMENT

WHAT IS THE GOAL OF NONOPERATIVE TREATMENT?

Nonoperative treatment aims to maintain a plantigrade foot, prevent the development of new ulcers, allow present ones to heal, enable the ability to weight bear with or without a brace and have the ability to wear diabetic shoes and maintain ambulation [**Figure 2**]. Total contact casting (TCC) remains the gold standard for nonoperative treatment, especially in the early stages. The length of time a patient will stay in a TCC will vary depending on the location of the deformity. Patients should generally remain in a TCC until osseous consolidation is achieved and after exiting the acute inflammatory phase. Following resolu-

Figure 2. 58-year-old female with type II diabetes and severe neuropathy presenting with rocker deformity (A) and plantar ulcer (B)

tion, patients may be fitted for a Charcot Restraint Orthotic Walker (CROW), hoping to eventually progress to customized orthoses or transition to a boot and, ultimately, shoes with inserts.[3]

HAS THE TRADITIONAL TCC EVOLVED?

Recent research aims to enhance TCC methods to improve patient satisfaction and reduce skin complications.[29,30] Removable cast walkers allow patients and physicians to perform regular skin examinations and modify the inner surface as needed.[31,32] However, recent research has argued that irremovable TCC is more economical and leads to better healing and quality-adjusted life-years.[31] Despite these findings, researchers have continued to explore ways to modify the traditional TCC to lessen skin complications and improve outcomes. Hopchlenert and Fischer recently created a bivalved TCC that allows only partial cast removal, creating a ventral window for viewing the foot.[33] De Souza *et al.* demonstrated that for treatment of acute CN Eichenholtz stage 1, immobilization with TCC is safe and allows patients to bear weight.[34] Much like removable cast walkers, their design allows physicians to perform regular wound checks while eliminating the risk of patient nonadherence.[33]

ARE PHARMACEUTICAL AGENTS EFFECTIVE?

Multiple pharmaceutical agents, such as bisphosphonates, calcitonin, and denosumab, have been proposed as possible treatments.[35,36] Of these agents, bisphosphonates have been the most extensively studied, and there is limited ev-

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idence to support their use.[37] Likewise, no studies have evaluated the effectiveness of daily intranasal calcitonin in improving patient-reported outcomes.[38]

More recently, Petrova *et al.* performed a randomized controlled study to assess the effect of recombinant human parathyroid hormone (PTH) on the resolution time of active CN.[39] Unfortunately, their study concluded that there was no difference in time to resolution.[39] However, additional studies have begun to investigate denosumab. In one observational study, fracture resolution time and time to clinical cessation were shorter in patients receiving denosumab.[35] Furthermore, a level III open-label trial found that patients receiving denosumab exited the acute inflammatory phase at an average of 52 days following injection, suggesting that it may be beneficial.[36] Overall, there is limited evidence to support the role of pharmacotherapy for earlier remission.[40]

OPERATIVE TREATMENT

WHAT IS THE GOAL OF OPERATIVE TREATMENT?

The goal of operative treatment is to obtain a stable, functional plantigrade foot, remove osteomyelitis, and prevent future ulceration and deformity. After determining surgical intervention is necessary, surgeons should work with other providers to optimize medical management after failing nonoperative management. In doing so, surgeons may consider using the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) risk calculator, which accurately predicts perioperative risk in CN patients undergoing reconstruction.[41] In addition, on multivariable analysis, longer lengths of stay were associated with low preoperative hemoglobin values (rate ratio [RR], 1.36; P = 0.01) and congestive heart failure (RR, 1.42; P = 0.02). Optimization of patients with diabetes and multiple medical comorbidities before elective Charcot reconstruction allows the surgery to be performed with a predictable risk for perioperative complications.[41]

WHEN IS SURGERY INDICATED?

In general, operative treatment is appropriate for patients with limb or life-threatening infection, who fail conservative management, or those with substantial deformities who are not amenable to bracing.[42] The optimal timing for surgery remains unclear. While it was traditionally not recommended to operate during the acute phase of the disease or in the setting of infection or ulceration, many experienced surgeons have challenged this belief.[42] A recent study demonstrated that tibiotalocalcaneal arthrodesis could be effective in patients with active hindfoot ulceration.[43] Most surgeons often operate on patients with active ulcers because the ulcers are slow to heal or recur quickly because of the deformity. Furthermore, Kavarthapu and Budair have had success utilizing a two-staged reconstruction method that does not require ulcer healing before proceeding to the second stage of internal fixation, which uses intramedullary nailing (IM) to stabilize the subtalar and ankle joints and a combination of lag screws, locking plates, and beams for the midfoot.[44] While more studies are needed to explore intervention in the active phase, these few studies are promising. Although, surgeons should still use caution when deciding how to manage a patient with active ulceration. A recent study by Wukich *et al.* that evaluated 245 patients with CN reported that a CN-related wound at presentation increased the likelihood of major amputation by a factor of 6.[45] Radiographic analysis in CN patients with ulceration can also be useful when stratifying the risk for both ulceration and the necessity for surgery.[32, 46] Nevertheless, surgical reconstruction has improved quality of life, necessitating further investigation into the optimal timing and indications.[47]

HOW DOES THE SEVERITY OF DEFORMITY INFLUENCE OPERATIVE STRATEGY?

In patients presenting with an otherwise stable foot who have excessive soft tissue breakdown from bony prominences, exostectomy can be effective.[48,49] While exostectomy has been reported to be effective with healing rates as high as 75%, a recent study cautioned against exostectomy confined to the lateral column, suggesting that it may increase the need for revision surgery because of calcaneal inclination change.[49] Likewise, in patients with severe equinus and a stable foot, Achilles tendon lengthening (ATL) has been effective, and a study by Tiruveedhula *et al.* found that ATL followed by weight-bearing TCC slowed and, in some cases, reduced midfoot CN.[50]

For patients with severe deformities not amenable to bracing, reconstruction can be achieved through arthrodesis using internal fixation osteotomies, external fixation, or a combination of both [**Figure 3**]. Multiple options exist for achieving a sound arthrodesis, including Kirschner wires, screws, plates, IM nails, beaming, and a superconstruct method.

Recently, an IM nail for hindfoot and ankle CN is a popular method. Moonot *et al.* reported that tibiotalocalcaneal nailing can effectively achieve a sound arthrodesis, even in patients presenting with severe loss of the talus.[51] Furthermore, a prospective cohort study of 61 patients treated with tibiotalocalcaneal arthrodesis with a retrograde IM nail reported only two cases of nonunion, improved American Orthopaedic Foot and Ankle Society (AOFAS)-hindfoot scores, and reduced pain.[52] Other authors have evaluated using an IM nail with an internal pseudoelastic nitinol compression element during tibiotalocalcaneal arthrodesis and reported a CT-based tibiotalar union of 71% in CN patients.[53] In addition to the IM nail, Pradana *et al.* recently demonstrated improvement in AOFAS-hindfoot scores by performing ankle arthrodesis using a double posterior lateral plating approach.[54]

Beaming is another popular method of correcting midfoot CN deformity, and a recent biomechanical study found it to provide a more robust construct when compared to plantar plating.[55] A case series by Santos-Vaquinhas *et al.* reported that 80% of patients treated with midfoot fusion with an IM beam and a lateral column bolt were ulcer-free and obtained a plantigrade foot. However, their work also reported high failure rates with complication and reoper-
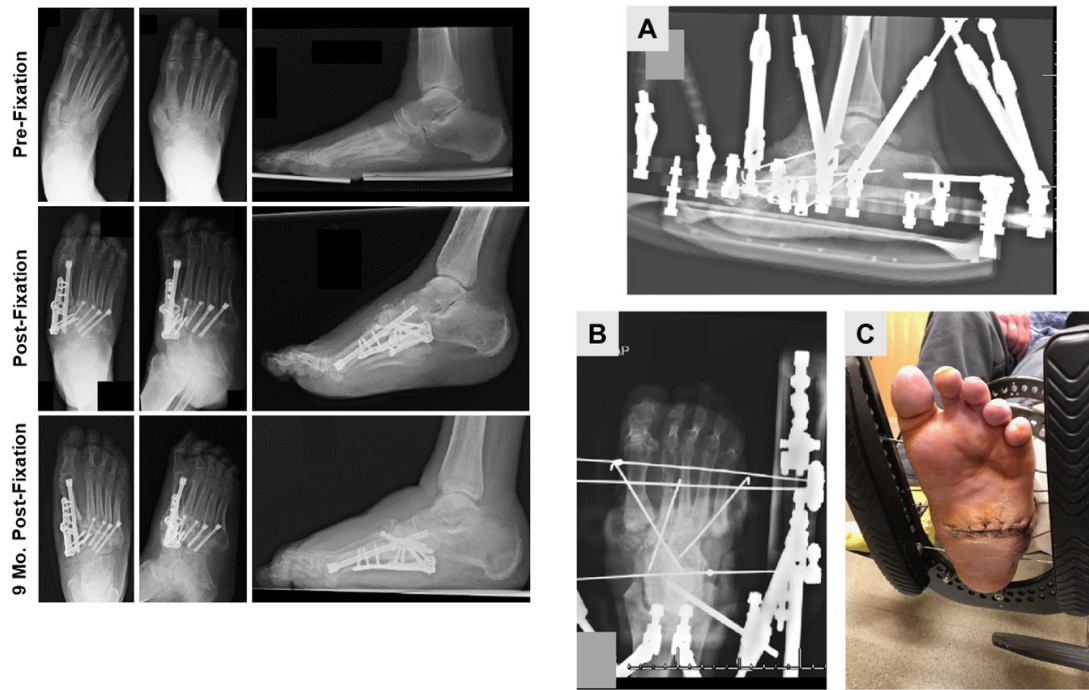
Figure 3. On the left is a 67-year-old female who presented with swelling after minimal trauma.

Treated initially in a walking cast, returned at four weeks with a Charcot, Lisfranc dislocation, and medial column collapse. The patient underwent midfoot stabilization and fusion; final radiographs at one year showed consolidation of the fusion mass. On the right is a 58-year-old female with Type II DM and neuropathy with a Charcot dislocation of the cuboid and a plantar ulcer. The patient underwent Illiazarov fixation application (A), reduction of dislocation (B), and rotational muscle flap closure (C). She was infection-free, and we salvaged the limb successfully.

ation rates of 80% and 40%, respectively.[56] Another study also reported an ulcer-free stable plantigrade foot in 84% of patients that underwent midfoot reconstruction with IM beaming, as well as improvements in Meary's angle and a 46% rate of midfoot union on final imaging.[57] Although, much like the aforementioned case study, high rates of complications, including deep infection and progression to amputation, were noted.[57]

The superconstruct technique has improved internal fixation by extending the IM beam into the unaffected joints. Recently, Manchanda *et al.* evaluated if the inclusion of the subtalar joint in the arthrodesis would be beneficial and reported a reduction in the odds of complication when subtalar arthrodesis was included during the reconstruction. Furthermore, they reported a negative correlation between the number of screws being used and the complication rate, suggesting that more hardware may be beneficial.[58]

One of the challenges associated with using the IM fusion bolts during stabilization of the medial column is their propensity to loosen and disrupt a sound reconstruction.[59] Consequently, Melhorn *et al.* evaluated a high-profile threaded fusion bolt (HTFB). They found patients treated with an HTFB had higher rates of bony consolidation after three months and improvements in Meary's angle after one year.[60]

Another difficult decision when performing internal fixation is figuring out what to do about the lateral column. Prior literature has suggested avoiding fusion of the lateral column during internal fixation to preserve the foot biomechanics. Interestingly, Derner *et al.* reported that lateral column arthrodesis in a non-neuropathic patient can pro-

vide pain relief and high rates of patient satisfaction, as well as low rates of revision in patients with post-traumatic degenerative joint disease and those with CN.[61]

Peritalar complex CN is exceptionally challenging and carries a high risk of amputation.[62] El-Mowafi *et al.* reported improved mean AOFAS scores and bony fusion in 29 of 38 feet using a combination of Ilizarov external fixation and plates and locked nails for internal fixation.[62] As such, a combined approach for patients with peritalar complex CN may be a viable option.

Over the last several years, external fixation has become a popular method because of its ability to be used in patients with active infection.[44] In 2021, Wirth *et al.* demonstrated its effectiveness for limb salvage, with the latter utilizing an Ilizarov fixator and finding positive results even in chronic osteomyelitis.[7] Moreover, closed arthrodesis with an Ilizarov ring external fixator is affordable compared to open approaches.[63]

A recent 7-14-year follow-up of 10 CN patients who presented with active ulceration and infection were treated with a Taylor Spatial Frame, which reported nine patients (9/10, 90%) were infection-free, ulcer free, and had a stable plantigrade foot amenable to diabetic footwear.[64] Additionally, El-Mowafi *et al.* reported high rates of clinical and radiographic union in patients that underwent a combination of retrograde IM nail and circular external fixation, leading to improvement in AOFAS scores for all 24 patients.[6]

While many have successfully used internal fixation, external fixation, or a combination of both, research has not found one method superior.[65] Yammine *et al.* performed a large meta-analysis to compare IM nailing with external

fixation. It concluded that IM nailing is better suited for patients with ulcers along the medial or lateral aspects of the sole or in patients who lacked ulceration altogether. In contrast, external fixation benefits patients with plantar ulcers to avoid the plantar approach for nail insertion.[8] Dayton *et al.* compared internal and external fixation complications and found that the odds of a successful outcome with internal fixation were 0.52 times greater than with external fixation.[66] Other approaches that have been proposed are the combined use of interlocked IM nails with ring external fixation and a midfoot wedge resection using a plantar approach to correct the rocker bottom deformity.[67,68]

WHAT OPERATIVE ADJUVANTS ARE BEING USED?

Several operative adjuvants can help improve patient outcomes. Niazi *et al.* demonstrated in a sample of 70 patients, of which nine were identified to have CN that the use of an adjuvant antibiotic-loaded absorbable bio-composite could help achieve cure rates in up to 90% of patients with concomitant foot ulcers and osteomyelitis.[69] Loveland *et al.* performed a retrospective multicenter case series examining the use of rhPDGF-BB/β-TCP graft to prevent nonunion in patients with CN that underwent joint fusion and found that the mean time to fusion is 13.09 ± 4.87 weeks. Only six patients were reported to have developed nonunion.[70]

COMPLICATIONS

The main complications that occur with nonoperative management are related to skin breakdown. At the same time, postoperative infection, re-ulceration, nonunion, hardware failure, and regaining the ability to walk are the main concerns following reconstruction procedures. Some research has estimated the 3-year mortality rate as 10.6%.[71] A 2022 retrospective study found that 38.7% of patients developed a new infection, 41.9% had new ulcers, and 19.4% went on to require a below-the-knee amputation, which carries its complications of phantom pain, difficulty with prosthesis fitting due to fluid shifts, and inability to ambulate without a prosthesis.[72] Sohn *et al.* described that CN alone does not pose an increased risk for amputation, but the risk is 12 times greater when a patient has ulceration.[73]

Anatomical location plays a role in outcomes and complication rates. In terms of functional recovery, patients who undergo ankle reconstructions have been found to have a 70% lower chance of returning to walking than patients who undergo reconstructions of the medial column. Patients are also 3.3 times as likely to undergo amputation compared to patients with reconstructions in the midfoot.[71] Additionally, another study that evaluated 223 feet that underwent operative correction reported that 7 patients died within a year of surgery, 15 underwent amputation, and of these patients, they found that those with a dislocation pattern or varus deformity were the least likely to achieve a favorable outcome.[74] Furthermore, Waibel *et al.* found an association between patients presenting with midfoot CN and the development of contralateral ulcers, suggesting the contralateral limb must be monitored.[75]

CONCLUSION AND AUTHORS' PREFERRED METHOD OF TREATMENT

Managing Charcot patients in our practice is dictated initially by staging and the presence of an ulcer and underlying infection. Based on our institution's pathologic staging research and cost-effective research data, we favor mid-tibia amputation for patients at high risk of complications from limb salvage surgery and who are also at high risk for failing limb salvage. In those without an ulcer, we begin with TCC to achieve a braceable, infection-free, plantigrade foot. The timing of surgery and method of internal fixation is highly dependent on host factors and is tailored individually to each patient. Patients who would benefit from reconstruction but are more likely to fail casting are taken to the operating room early, regardless of clinical stage. Those with an ulcer but less likely to undergo amputation undergo a staged reconstruction with debridement, Ilizarov frame application, and deformity correction with staged reconstruction once the ulcer is closed and the patient is clear of infection before implanting hardware. Lastly, a multidisciplinary approach, including infectious disease specialists in the clinic, a therapist trained at TCC, and medical doctors skilled at glycemic control, is essential for achieving paramount success in treating Charcot. Hopefully, as clinical research becomes more available, we can use best practice guidelines to tailor our approach more systematically, which is most effective for patients and our health system.

REFERENCES

1. Albright RH, Joseph RM, Wukich DK, Armstrong DG, Fleischer AE. Is Reconstruction of Unstable Midfoot Charcot Neuroarthropathy Cost Effective from a US Payer's Perspective? *Clin Orthop Relat Res*. 2020;478(12):2869-2888. doi:10.1097/corr.0000000000001416

2. Labovitz JM, Shapiro JM, Satterfield VK, Smith NT. Excess Cost and Healthcare Resources Associated With Delayed Diagnosis of Charcot Foot. *J Foot Ankle Surg*. 2018;57(5):952-956. doi:10.1053/j.jfas.2018.03.036

3. Dardari D. An overview of Charcot's neuroarthropathy. *J Clin Transl Endocrinol*. 2020;22(100239):100239. doi:10.1016/j.jcte.2020.100239

4. King J, Murie B, Fanburg-Smith JC, et al. Novel FEMASK-score, a histopathologic assessment for destructive Charcot neuropathic arthropathy, reveals intraneural vasculopathy and correlates with progression and best treatment. *Ann Diagn Pathol*. 2020;47(151509):151509. doi:10.1016/j.anndiagpath.2020.151509

5. Koroneos Z, Ptasinski A, Stauch CM, Luick LR, Fanburg-Smith JC, Aynardi MC. Establishment of a Neurodegenerative Mouse Model for Charcot Neuropathic Arthropathy. *Foot Ankle Orthop*. 2022;7(1):2473011421S0028. doi:10.1177/2473011421s00287

6. El-Mowafi H, Abulsaad M, Kandil Y, El-Hawary A, Ali S. Hybrid Fixation for Ankle Fusion in Diabetic Charcot Arthropathy. *Foot Ankle Int*. 2018;39(1):93-98. doi:10.1177/1071100717735074

7. Wirth SH, Viehöfer AF, Tondelli T, et al. Mid-term walking ability after Charcot foot reconstruction using the Ilizarov ring fixator. *Arch Orthop Trauma Surg*. 2020;140(12):1909-1917. doi:10.1007/s00402-020-03407-5

8. Yammine K, Assi C. Intramedullary nail versus external fixator for ankle arthrodesis in Charcot neuroarthropathy: A meta-analysis of comparative studies. *J Orthop Surg (Hong Kong)*. 2019;27(2):230949901983601. doi:10.1177/2309499019836012

9. Marmolejo VS, Arnold JF, Ponticello M, Anderson CA. Charcot Foot: Clinical Clues, Diagnostic Strategies, and Treatment Principles. *Am Fam Physician*. 2018;97(9):594-599. http://www.ncbi.nlm.nih.gov/pubmed/29763252

10. Jansen RB, Jørgensen B, Holstein PE, Møller KK, Svendsen OL. Mortality and complications after treatment of acute diabetic Charcot foot. *J Diabetes Complications*. 2018;32(12):1141-1147. doi:10.1016/j.jdiacomp.2018.09.013

11. Cascini S, Agabiti N, Davoli M, et al. Survival and factors predicting mortality after major and minor lower-extremity amputations among patients with diabetes: a population-based study using health information systems. *BMJ Open Diab Res Care*. 2020;8(1):e001355. doi:10.1136/bmjdrc-2020-001355

12. Yammine K, Boulos K, Assi C, Hayek F. Amputation and mortality frequencies associated with diabetic Charcot foot arthropathy: a meta-analysis. *Foot and Ankle Surgery*. 2022;28(8):1170-1176. doi:10.1016/j.fas.2022.08.004

13. Petrova NL, Dew TK, Musto RL, et al. Inflammatory and bone turnover markers in a cross-sectional and prospective study of acute Charcot osteoarthropathy. *Diabet Med*. 2014;32(2):267-273. doi:10.1111/dme.12590

14. M. NF, A. H, J. T, N. S. The effect of polyneuropathy on foot microcirculation in Type II diabetes. *Diabetologia*. 2002;45(8):1164-1171. doi:10.1007/s00125-002-0872-z

15. Folestad A, Ålund M, Asteberg S, et al. Offloading treatment is linked to activation of proinflammatory cytokines and start of bone repair and remodeling in Charcot arthropathy patients. *J Foot Ankle Res*. 2015;8(1):72. doi:10.1186/s13047-015-0129-y

16. Bruhn-Olszewska B, Korzon-Burakowska A, Węgrzyn G, Jakóbkiewicz-Banecka J. Prevalence of polymorphisms in OPG, RANKL and RANK as potential markers for Charcot arthropathy development. *Sci Rep*. 2017;7(1):501. doi:10.1038/s41598-017-00563-4

17. Mitchell R, Molligan J, Rooney S, Cho Y, Schon L, Zhang Z. Functionally compromised synovium-derived mesenchymal stem cells in Charcot neuroarthropathy. *Exp Mol Pathol*. 2018;104(1):82-88. doi:10.1016/j.yexmp.2018.01.003

18. Pasquier J, Ramachandran V, Abu-Qaoud MR, et al. Differentially expressed circulating microRNAs in the development of acute diabetic Charcot foot. *Epigenomics*. 2018;10(10):1267-1278. doi:10.2217/epi-2018-0052

19. Guo Y, Schon LC, Paudel S, Feltham T, Manandhar L, Zhang Z. Calcitonin Gene-Related Peptide in Charcot Foot Neuroarthropathy. *Foot Ankle Orthop*. 2022;7(1):2473011421S0022. [doi:10.1177/2473011421s00220](doi:10.1177/2473011421s00220)

20. Short DJ, Zgonis T. Medical Imaging in Differentiating the Diabetic Charcot Foot from Osteomyelitis. *Clinics in Podiatric Medicine and Surgery*. 2017;34(1):9-14. [doi:10.1016/j.cpm.2016.07.002](doi:10.1016/j.cpm.2016.07.002)

21. Schmidt BM. Clinical insights into Charcot foot. *Best Pract Res Clin Rheumatol*. 2020;34(3):101563. doi:10.1016/j.berh.2020.101563

22. Chantelau E, Richter A, Schmidt-Grigoriadis P, Scherbaum W. The diabetic charcot foot: MRI discloses bone stress injury as trigger mechanism of neuroarthropathy. *Exp Clin Endocrinol Diabetes*. 2006;114(03):118-123. [doi:10.1055/s-2006-924026](doi:10.1055/s-2006-924026)

23. Ahluwalia R, Bilal A, Petrova N, et al. The Role of Bone Scintigraphy with SPECT/CT in the Characterization and Early Diagnosis of Stage 0 Charcot Neuroarthropathy. *JCM*. 2020;9(12):4123. [doi:10.3390/jcm9124123](doi:10.3390/jcm9124123)

24. Rosskopf AB, Loupatatzis C, Pfirrmann CWA, Böni T, Berli MC. The Charcot foot: a pictorial review. *Insights Imaging*. 2019;10(1):77. [doi:10.1186/s13244-019-0768-9](doi:10.1186/s13244-019-0768-9)

25. Lauri C, Tamminga M, Glaudemans AWJM, et al. Detection of Osteomyelitis in the Diabetic Foot by Imaging Techniques: A Systematic Review and Meta-analysis Comparing MRI, White Blood Cell Scintigraphy, and FDG-PET. *Diabetes Care*. 2017;40(8):1111-1120. [doi:10.2337/dc17-0532](doi:10.2337/dc17-0532)

26. Kavarthapu V, Vris A. Charcot midfoot reconstruction—surgical technique based on deformity patterns. *Ann Joint*. 2020;5:28-28. [doi:10.21037/aoj.2020.02.01](doi:10.21037/aoj.2020.02.01)

27. Wukich DK, Raspovic K, Liu GT, et al. Are the Sanders-Frykberg and Brodsky-Trepman Classifications Reliable in Diabetic Charcot Neuroarthropathy? *J Foot Ankle Surg*. 2021;60(3):432-435. doi:10.1053/j.jfas.2020.03.003

28. Rogers LC, Frykberg RG, Armstrong DG, et al. The Charcot foot in diabetes. *Diabetes care*. 2011;34(9):2123-2129. [doi:10.2337/dc11-0844](doi:10.2337/dc11-0844)

29. Riopelle A, LeDuc R, Wesolowski M, Schiff AP, Pinzur MS. Risk of Complications With the Total Contact Cast in Diabetic Foot Disorders. *Foot Ankle Spec*. 2021;14(1):25-31. [doi:10.1177/1938640019895920](doi:10.1177/1938640019895920)

30. Saltzman CL, Hagy ML, Zimmerman B, Estin M, Cooper R. How effective is intensive nonoperative initial treatment of patients with diabetes and Charcot arthropathy of the feet? *Clinical Orthopaedics and Related Research*. 2005;(435):185-190. [doi:10.1097/00003086-200506000-00026](doi:10.1097/00003086-200506000-00026)

31. Health Quality Ontario. Fibreglass Total Contact Casting, Removable Cast Walkers, and Irremovable Cast Walkers to Treat Diabetic Neuropathic Foot Ulcers: A Health Technology Assessment. *Ont Health Technol Assess Ser*. 2017;17(12):1-124. http://www.ncbi.nlm.nih.gov/pubmed/28989556

32. Parisi MCR, Godoy-Santos AL, Ortiz RT, et al. Radiographic and functional results in the treatment of early stages of Charcot neuroarthropathy with a walker boot and immediate weight bearing. *Diabetic Foot & Ankle*. 2013;4(1):22487. [doi:10.3402/dfa.v4i0.22487](doi:10.3402/dfa.v4i0.22487)

33. Hochlenert D, Fischer C. Ventral Windowed Total Contact Casts Safely Offload Diabetic Feet and Allow Access to the Foot. *J Diabetes Sci Technol*. 2022;16(1):137-143. [doi:10.1177/1932296820964069](doi:10.1177/1932296820964069)

34. de Souza LJ. Charcot arthropathy and immobilization in a weight-bearing total contact cast. *The Journal of Bone and Joint Surgery-American Volume*. 2008;90(4):754-759. doi:10.2106/jbjs.f.01523

35. Busch-Westbroek TE, Delpeut K, Balm R, et al. Effect of Single Dose of RANKL Antibody Treatment on Acute Charcot Neuro-osteoarthropathy of the Foot. *Diabetes Care*. 2018;41(3):e21-e22. [doi:10.2337/dc17-1517](doi:10.2337/dc17-1517)

36. Shofler D, Hamedani E, Seun J, et al. Investigating the Use of Denosumab in the Treatment of Acute Charcot Neuroarthropathy. *J Foot Ankle Surg*. 2021;60(2):354-357. doi:10.1053/j.jfas.2020.09.018

37. Richard JL, Almasri M, Schuldiner S. Treatment of acute Charcot foot with bisphosphonates: a systematic review of the literature. *Diabetologia*. 2012;55(5):1258-1264. [doi:10.1007/s00125-012-2507-3](doi:10.1007/s00125-012-2507-3)

38. Bem R, Jirkovská A, Fejfarová V, Skibová J, Jude EB. Intranasal calcitonin in the treatment of acute Charcot neuroosteoarthropathy: a randomized controlled trial. *Diabetes care*. 2006;29(6):1392-1394. [doi:10.2337/dc06-0376](doi:10.2337/dc06-0376)

39. Petrova NL, Donaldson NK, Bates M, et al. Effect of Recombinant Human Parathyroid Hormone (1-84) on Resolution of Active Charcot Neuro-osteoarthropathy in Diabetes: A Randomized, Double-Blind, Placebo-Controlled Study. *Diabetes Care*. 2021;44(7):1613-1621. [doi:10.2337/dc21-0008](doi:10.2337/dc21-0008)

40. Rastogi A, Bhansali A, Jude EB. Efficacy of medical treatment for Charcot neuroarthropathy: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol*. 2021;58(6):687-696. doi:10.1007/s00592-020-01664-9

41. Lyons M, McGregor PC, Pinzur MS, Adams W, Wilkos-Prostran L. Risk Reduction and Perioperative Complications in Patients With Diabetes and Multiple Medical Comorbidities Undergoing Charcot Foot Reconstruction. *Foot Ankle Int*. 2021;42(7):902-909. doi:10.1177/1071100721995422

42. Mittlmeier T, Klaue K, Haar P, Beck M. Should one consider primary surgical reconstruction in charcot arthropathy of the feet? *Clinical Orthopaedics & Related Research*. 2010;468(4):1002-1011. doi:10.1007/s11999-009-0972-x

43. Hoch CP, Newton W, Newton W, Gross CE, Scott DJ. Effect of Preoperative Ulceration on Outcomes of Tibiotalocalcaneal Arthrodesis. *Foot Ankle Orthop* . 2022;7(1):2473011421S0024. doi:10.1177/2473011421s00244

44. Kavarthapu V, Budair B. Two-stage reconstruction of infected Charcot foot using internal fixation : a promising functional limb salvage technique. *Bone Joint J*. 2021;103-B(10):1611-1618. doi:10.1302/0301-620x.103b10.bjj-2021-0339.r2

45. Wukich DK, Sadoskas D, Vaudreuil NJ, Fourman M. Comparison of Diabetic Charcot Patients With and Without Foot Wounds. *Foot Ankle Int*. 2017;38(2):140-148. doi:10.1177/1071100716673985

46. Wukich DK, Raspovic KM, Hobizal KB, Rosario B. Radiographic analysis of diabetic midfoot charcot neuroarthropathy with and without midfoot ulceration. *Foot Ankle Int*. 2014;35(11):1108-1115. doi:10.1177/1071100714547218

47. Kroin E, Chaharbakhshi EO, Schiff A, Pinzur MS. Improvement in Quality of Life Following Operative Correction of Midtarsal Charcot Foot Deformity. *Foot Ankle Int*. 2018;39(7):808-811. doi:10.1177/1071100718762138

48. Brodsky JW, Rouse AM. Exostectomy for symptomatic bony prominences in diabetic charcot feet. *Clinical Orthopaedics and Related Research*. 1993;296:21-26. doi:10.1097/00003086-199311000-00005

49. Molines-Barroso RJ, Lázaro-Martínez JL, Beneit-Montesinos JV, Álvaro-Afonso FJ, García-Morales E, García-Álvarez Y. Early Foot Structural Changes After Lateral Column Exostectomy in Patients With Charcot Foot. *Int J Low Extrem Wounds*. 2019;18(2):129-134. doi:10.1177/1534734619848553

50. Tiruveedhula M, Graham A, Thapar A, Dindyal S, Mulcahy M. Outcomes of Tendo-Achilles lengthening and weight-bearing total contact cast for management of early midfoot charcot neuroarthropathy. *J Clin Orthop Trauma*. 2021;17:128-138. doi:10.1016/j.jcot.2021.03.001

51. Moonot P, Sharma G, Kadakia A. Functional outcome in patients with Charcot neuropathy with almost complete loss of talus treated by tibio-talo calcaneal nail: A cross-sectional study. *Foot*. 2021;49(101833):101833. doi:10.1016/j.foot.2021.101833

52. Perez-Aznar A, Gonzalez-Navarro B, Bello-Tejeda LL, Alonso-Montero C, Lizaur-Utrilla A, Lopez-Prats FA. Tibiotalocalcaneal arthrodesis with a retrograde intramedullary nail: a prospective cohort study at a minimum five year follow-up. *Int Orthop*. 2021;45(9):2299-2305. doi:10.1007/s00264-020-04904-3

53. Ford SE, Kwon JY, Ellington JK. Tibiotalocalcaneal Arthrodesis Utilizing a Titanium Intramedullary Nail With an Internal Pseudoelastic Nitinol Compression Element: A Retrospective Case Series of 33 Patients. *J Foot Ankle Surg*. 2019;58(2):266-272. doi:10.1053/j.jfas.2018.08.046

54. Pradana AS, Phatama KY, Mustamsir E, Cahyono GD, Oktafandi GINAA, Hidayat M. Double posterior lateral plating arthrodesis for charcot ankle: A case series. *Ann Med Surg*. 2021;65(102250). doi:10.1016/j.amsu.2021.102250

55. Simonik MM, Wilczek J, LaPorta G, Willing R. Biomechanical Comparison of Intramedullary Beaming and Plantar Plating Methods for Stabilizing the Medial Column of the Foot: An In Vitro Study. *J Foot Ankle Surg*. 2018;57(6):1073-1079. doi:10.1053/j.jfas.2018.03.043

56. Dos Santos-Vaquinhas A, Parra G, Martínez P, Sobrón B, Cuervas-Mons M. Beaming in the Charcot foot: A case series with 12-month minimum follow-up. *Foot*. 2021;47(101814):101814. doi:10.1016/j.foot.2021.101814

57. Ford SE, Cohen BE, Davis WH, Jones CP. Clinical Outcomes and Complications of Midfoot Charcot Reconstruction With Intramedullary Beaming. *Foot Ankle Int*. 2018;40(1):18-23. doi:10.1177/1071100718799966

58. Manchanda K, Wallace SB, Ahn J, et al. Charcot Midfoot Reconstruction: Does Subtalar Arthrodesis or Medial Column Fixation Improve Outcomes? *J Foot Ankle Surg*. 2020;59(6):1219-1223. doi:10.1053/j.jfas.2020.07.001

59. Eschler A, Wussow A, Ulmar B, Mittlmeier T, Gradl G. Intramedullary medial column support with the Midfoot Fusion Bolt (MFB) is not sufficient for osseous healing of arthrodesis in neuroosteoarthropathic feet. *Injury*. 2014;45:S38-S43. doi:10.1016/j.injury.2013.10.037

60. Mehlhorn AT, Ugland KI, Hörterer H, Gottschalk O, Südkamp N, Walther M. A high-profile thread with grit-blasted and acid-etched surface reduces loosening of medial column fusion bolt in instable Charcot foot. *Foot Ankle Surg*. 2020;26(6):637-643. doi:10.1016/j.fas.2019.08.004

61. Derner R, Derner BS, Olsen A. Fusion of the Tarsometatarsal Joints: A Focus on Lateral Column Fusion Nonunion Rates. *J Foot Ankle Surg*. 2020;59(4):704-710. doi:10.1053/j.jfas.2019.12.004

62. El-Mowafi H, El-Hawary A, Kandil Y. Functional pedal construct achieved by combined operative treatment in peritalar complex Charcot arthropathy: A prospective study of 38 feet. *Foot Ankle Surg*. 2018;24(3):236-241. doi:10.1016/j.fas.2017.02.011

63. Alammar Y, Sudnitsyn A, Neretin A, Leonchuk S, Kliushin NM. Closed arthrodesis in infected neuropathic ankles using Ilizarov ring fixation. *Bone Joint J*. 2020;102-B(4):470-477. doi:10.1302/0301-620x.102b4.bjj-2019-1158.r1

64. Lahoti O, Abhishetty N, Shetty S. Correction of Foot Deformities from Charcot Arthropathy with the Taylor Spatial Frame: A 7–14-year Follow-up. *Strategies in Trauma and Limb Reconstruction*. 2021;16(2):96-101. doi:10.5005/jp-journals-10080-1525

65. Ha J, Hester T, Foley R, et al. Charcot foot reconstruction outcomes: A systematic review. *J Clin Orthop Trauma*. 2020;11(3):357-368. doi:10.1016/j.jcot.2020.03.025

66. Dayton P, Feilmeier M, Thompson M, Whitehouse P, Reimer RA. Comparison of Complications for Internal and External Fixation for Charcot Reconstruction: A Systematic Review. *The Journal of Foot and Ankle Surgery*. 2015;54(6):1072-1075. doi:10.1053/j.jfas.2015.06.003

67. Tomczak C, Beaman D, Perkins S. Combined Intramedullary Nail Coated With Antibiotic-Containing Cement and Ring Fixation for Limb Salvage in the Severely Deformed, Infected, Neuroarthropathic Ankle. *Foot Ankle Int*. 2018;40(1):48-55. doi:10.1177/1071100718800836

68. Persky JD, Langan T, Smith CN, Burns PR. Plantar Approach for Midfoot Wedge Resection to Reconstruct the Rocker Bottom Foot. *J Foot Ankle Surg*. 2019;58(5):1030-1035. doi:10.1053/j.jfas.2019.01.004

69. Niazi NS, Drampalos E, Morrissey N, Jahangir N, Wee A, Pillai A. Adjuvant antibiotic loaded bio composite in the management of diabetic foot osteomyelitis — A multicentre study. *Foot*. 2019;39:22-27. doi:10.1016/j.foot.2019.01.005

70. Loveland JD, McMillen RL, Cala MA. A Multicenter, Retrospective, Case Series of Patients With Charcot Neuroarthropathy Deformities Undergoing Arthrodesis Utilizing Recombinant Human Platelet-derived Growth Factor With Beta-Tricalcium Phosphate. *J Foot Ankle Surg*. 2021;60(1):74-79. doi:10.1053/j.jfas.2020.08.030

71. McCann L, Zhu S, Pollard JD, Ritterman Weintraub ML, Dickinson JD. Success and Survivorship Following Charcot Reconstruction: A Review of 151 Cases. *J Foot Ankle Surg*. 2021;60(3):535-540. doi:10.1053/j.jfas.2020.04.022

72. Pattisapu N, Bettin CC, Yeoh JC, Sarfani S. Reconstructive Surgical Management of Charcot Neuropathy of the Foot and Ankle: A Retrospective Study. *Foot Ankle Orthop*. 2022;7(1):2473011421S0039. doi:10.1177/2473011421s00395

73. Sohn MW, Stuck RM, Pinzur M, Lee TA, Budiman-Mak E. Lower-extremity amputation risk after charcot arthropathy and diabetic foot ulcer. *Diabetes care*. 2009;33(1):98-100. doi:10.2337/dc09-1497

74. Pinzur MS, Schiff AP. Deformity and Clinical Outcomes Following Operative Correction of Charcot Foot: A New Classification With Implications for Treatment. *Foot Ankle Int*. 2017;39(3):265-270. doi:10.1177/1071100717742371

75. Waibel FWA, Berli MC, Gratwohl V, et al. Midterm Fate of the Contralateral Foot in Charcot Arthropathy. *Foot Ankle Int*. 2020;41(10):1181-1189. doi:10.1177/1071100720937654