THE CARE OF THE DIABETIC FOOT

The first principle in the care of the diabetic foot is to recognize the primacy of prophylactic care. Indeed, an ounce of prevention is worth the proverbial pound of cure, even in the apparent low risk patient without obvious peripheral neuropathy or vasculopathy. Physicians and other health care professionals have a critically important role to play in educating diabetics regarding daily foot care with attention to skin, nail and callus care, proper footwear and strategies to prevent foot trauma and infection. Diabetes remains the commonest cause of non-traumatic limb loss, not to mention the suffering and economic impact of managing chronic diabetic foot pain and sepsis. Two-thirds of diabetic amputations follow complications related to foot ulcers.

In the late 1990s, up to 3,500 lower extremity amputations were performed in diabetics in Canada and over 80,000 in the USA compared with 50,000/year in the 1980s. According to the Canadian Diabetes Association and turn of the millennium statistics, approximately 5 – 10% of diabetics will develop a foot ulcer, and of those, about 15 – 25% will require a leg or partial foot amputation. American reports suggest a 20% amputation rate with these patients. About 20% of patients requiring below-knee amputations do not adequately heal their surgical wounds and required further wound revision surgery or progression to an above-knee amputation. There is a 50% 5-year rate of amputation of the contralateral limb once a patient has had an above- or below-knee amputation. Following first amputation there is a 40% 5-year survival only for this group, death largely from heart attack, stroke or further complications of the remaining foot. Vascular and neuropathic ulcers account for greater than 25% of the health care costs of diabetic complications. The typical cost of an amputation ranges from $30,000 to $35,000, while the average cost of diabetic ulcer care is approximately $4,600. Full-thickness ulcer care costs approximately $2,000, while those down to bone and joint approximately $15,000. A 2001 costing study in the United States disclosed costs of $9,300 for uninfected ulcers, $24,600 for infected ulcers and $45,000 for ulcers complicated with osteomyelitis.

Ulcer prevalence in diabetics is approximately 6.5 per 1000 over the age of 45 years and 10.3 per 1000 older than 75 years. More than 80% of diabetic amputations are preceded by an ulcer and diabetics account for in excess of 60% of non-traumatic amputations. Unfortunately education alone does not reduce the burden of illness, unless there is an intervention, according to a Cochrane review.

As of 2007, there were over 800,000 diabetics in Ontario with an incidence of 50,000 or more new cases annually. Canada’s Institute for Evaluative Studies reported (Lancet, March 2007) that 9% of Ontarians more than 20 years of age were diabetic (greater than 90% being type-2) up from 5.2% in 1995. The WHO projected a 6.4% worldwide
prevalence rate (8.4% for developed countries) by 2030. This is linked to the “diabesity” epidemic. Between 1995 and 2005 the prevalence rates doubled from 1.8% to 3.5% in the 20 – 49 year cohort and 10.6 to 17.1% in the older than 50. As of 2012, about 10% of Ontarians were diabetic (more than 1,200,000).

Amongst First Nations there is an annual amputation rate of 7/1000 diabetics compared with 2/1000 per year amputations for the Non-First Nations’ diabetics. Since the mid-1990s there has been a significant reduction in local toe and metatarsal amputations, but no change in the 10-year rate of above and below-knee amputations. At the millennium diabetics in Ontario faced, on average, a 12-year reduction in life expectancy: diabetic females from 81 to 68 years and male diabetics from 77 to 65 years.

It is said that somewhere in the world every 30 minutes, a lower extremity amputation is performed for trauma from stepping on a landmine. It is said that somewhere in the world every 30 seconds, a lower extremity amputation is performed on a diabetic.

Pressure platform studies demonstrate a diminished load on the toes as an early finding in diabetic neuropathy. The reduction in toe load leads to a corresponding increase in metatarsal head loads along with a shift of forefoot loading away from the medial side with increasing load now borne under the mid-foot, characteristic of weakness of the longitudinal arch (mid-tarsal loading). Diabetics therefore bear excessive weight on the plantar aspects of their feet in locations not designed for such loads.

Neurologic, vascular and musculoskeletal abnormalities are the predominant risk factors, in addition to metabolic and immunologic abnormalities that impede wound healing and enhance infectious complications.

It has been commonly observed that diabetes is often “a disease of denial” with patients indifferent to their weight, glucose control and foot-care, often leading to lower extremity complications, particularly in the patient who has lost plantar protective sensation.

**VASCULAR DISEASE:**

Atherosclerosis accounts for 80% of all diabetes-related mortality. Coronary artery deaths account for 75% of this group, while the remainder is related to stroke or peripheral vascular disease. It is estimated that 50% of newly diagnosed diabetics already have coronary artery disease. Risk of cardiovascular events is increased threefold in men and fourfold in women with Type II diabetes and in the Framingham Heart Study, the age-adjusted risk ratio for manifestations of cardiovascular disease were 2.60 for diabetic women and 5.27 for diabetic men, compared with non-diabetic persons.

Diabetic ulceration may be predisposed by vascular insufficiency in a cool foot with diminished peripheral pulses and associated trophic changes. Vascular ulcers are often not on weight bearing surfaces. Atherosclerosis in diabetics is most commonly femoral popliteal as in non-diabetics. Similarly, age at amputation for ischemia is in the early 70s for both diabetic and non-diabetic patients with oblitative atherosclerotic disease.
However, tibial and peroneal arterial atherosclerotic occlusion is almost a sine qua non of diabetic atherosclerosis. Normal distal pulses in diabetes excludes clinically significant occlusive vascular disease. Small vessel disease or micro-vascular occlusive disease in diabetics is not an important entity from the standpoint of gangrene, however, may play a role in wound healing and neuropathic ulcer healing. One can have an ischemic foot with strong popliteal pulses and ischemic toes with palpable dorsalis pedis and posterior tibialis pulses. Therefore, transcutaneous oxygen measurements (TCOM) and skin perfusion pressures (SPP) are helpful to assess skin and toe wound healing potential. Isolated tibial artery occlusive disease is usually associated with reasonable foot circulation. Absent pulses, a cool often hyperemic foot with thin skin and pallor on elevation predict for severe peripheral arterial disease.

Clinically manifest atherosclerosis occurs five to ten times more commonly in diabetic patients than non-diabetics. Burning, shooting, disabling nocturnal pain of diabetic neuropathy may be difficult to distinguish from atypical ischemic rest pain. Symmetrical distribution, as well as failure to be relieved by dependency of the foot favours neuropathy over critical limb ischemia.

A single cigarette of tobacco smoked may reduce perfusion in the limbs by 30% with an effect that persists for up to one hour. The toxicity therefore of tobacco smoking is synergistic with the adverse vascular affect of diabetes itself.

Diabetic gangrene is seen in the setting of foot edema in two-thirds of cases and its typical distribution is approximately 65% to the digits, 15% at the heel, 10% on the dorsum and 10% under the metatarsal heads.

Arterial insufficiency is a pathogenic factor in up to 60% of diabetics with non-healing ulcers and 45% going on to amputation.

Diabetics with claudication have a much higher risk of progression to gangrene than do stable non-diabetic claudicants. Claudication is 3.8 times more frequent in diabetic males, and 6.5 times more frequent in diabetic females than non-diabetics. Peripheral arterial disease in diabetics is a marker for coronary artery disease and carries a fourfold increased risk for myocardial infarction and stroke.

Atherosclerosis obliterans is particularly accelerated in the smoking diabetic. Smoking cessation is the most important modifiable risk factor for occlusive vascular disease in diabetics.

Calcification in the distal vessels is characteristic of diabetic atherosclerosis and may be seen on radiographs of the foot or felt on palpation of the dorsalis pedis artery. The pulse is preserved frequently in these calcified vessels, which may be non-compressible when using a blood pressure cuff to estimate ankle pressures. Calcification of pedal vessels is reported to occur in up to one-quarter of diabetic patients. The ratio of ankle to brachial blood pressures (Ankle-Brachial Index) provides a rough estimate of vascular risk as well as healing. Indices of approximately 0.5 to 0.7 indicate moderate to severe occlusive
disease. Distal amputations heal in over 90% when the ABI exceeds 0.45 in diabetics. An ABI in excess of 1.2 implies non-compressibility from vascular calcification and is therefore not a reliable indicator of actual perfusion. Similarly, transcutaneous oximetry (available only in vascular laboratories and hyperbaric chambers) predicts risk with abnormal values being less than 40 mm Hg. (0 to 15 represents severe, and 15 to 25 moderately severe disease.) 90% of distal amputees will heal with transcutaneous oxygen tensions in excess of 30 mm Hg; 70% with tensions between 20 and 30 mm Hg; and, less than 50% when pressures fall below 20 mm Hg. TcpO2 of less than 30mmHg predicts for non-healing of ulcers. The TcpO2 on 100% oxygen should rise to 200 – 400 in normal patients, 40 – 100 in moderately impaired and less than 40 in severely impaired circulation. A low TcpO2 that does not rise on inhaled 100% oxygen implies no role for hyperbaric oxygen therapy.

Progressive amputation follows minor distal amputations in about 20% of diabetics within six months. With lesions affecting one toe, local amputation offers an immediate one in three chance of limb salvage, with greater than 80% coming to amputation within one year. Limited amputation is much more difficult if more than one toe is involved. Transverse metatarsal amputation is possible if distal vessel reconstruction can be performed. Distal foot autogenous venous bypass grafts have close to 90% three-year patency, and 90% sparing of amputation.

Mid-tarsal and Symes amputations in diabetics are usually unsuccessful, while below-knee amputation is problematic and to be avoided if neuropathic calf skin and muscle is used to cover the end of the stump. Therefore, in severe extensive neuropathy an above-knee amputation is often the amputation of choice.

Dependent rubor and pallor on elevation are typical signs of peripheral vascular disease to look for along with capillary refill times over the toes delayed beyond 4 seconds. Ischemia aggravated by elevation of the feet more than 6 inches in a supine patient is indicative of severe disease, while pressure from peripheral edema further compromises the circulation.

Peripheral ischemic disease may be treated with cardio-synchronous pneumatic compression with the use of the Circulator Boot (Biomation 1-888-667-2324, www.biomation.com). Hammersmith Hospital has also reported the development of Artassist for claudication. This is a pneumatic calf compression with inflations three times per minute for three hours daily over 6 months. Five-percent of the diabetic population over the age of 70 have claudication from proximal arterial disease. With Artassist patients were capable of walking 2.5 times as far as their pre-treatment claudication permitted. Diabetics may have proximal atherosclerotic occlusive disease and recent studies suggest that Paclitaxol eluting balloons for angioplasty of the superficial femoral and popliteal arteries may be more effective than standard angioplasties.

Diabetics and non-diabetics perform equivalently for each type of vascular intervention. Limb salvage rates are as high as 95% at 2 years for percutaneous angioplasties for
critical limb ischemia patients over the age of eighty. Five year limb salvage rates for infra-inguinal revascularization surgery exceed 85% in the greater than 70 year age group with close to 65% five year survival in those under eighty, and 55% in those 80 – 90 years of age.

Cilostazol is thought to be superior to pentoxifylline (Trental) and when combined with a supervised exercise walking program is superior to either alone in improving walking distances.

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THE DIABETIC PERIPHERAL NEUROPATHIES:

Hypertension, albuminemia and any degree of retinopathy have a much higher association with neuropathy in diabetics, suggesting a common pathogenic mechanism. High BMI has a weaker association with retinopathy but incidence rates for developing diabetes are reduced by 20% by reducing waist circumference (visceral fat) by 2.5cm. In younger non-obese Type 1 diabetics followed for 7 years, 30% were noted to have neuropathy at intake with a further 25% acquiring neuropathy by 7 years. There are a host of neuropathic lower extremity syndromes that diabetics are prone to both individually and in combination.

These include:

1. Sensory polyneuropathy clinically encompassing a spectrum from subclinical sensory loss to the totally asensate foot (distal symmetric small fibre neuropathy).
2. Autonomic neuropathy with trophic changes, distal hair loss and dry skin.
3. Sensory motor polyneuropathy with distal weakness of longer duration (much less common than sensory neuropathy).
4. Painful distal sensory neuropathy.
5. Painful proximal diabetic neuropathy or lumbosacral radiculoplexus neuropathy.
6. Femoral neuropathy with diabetic amyotrophy associated with quadriceps wasting.
8. Single neuropathy especially of the peroneal and posterior tibialis nerve; third nerve, intercostal nerve roots and median nerve (mononeuropathy).
9. Local pressure palsies and entrapment neuropathies.
10. Part of the syndrome of mononeuritis multiplex
11. Chronic inflammatory demyelinating polyneuropathy.
12. Restless legs syndrome associated with diabetes.
Autonomic disease leads often to diminished sweating with brittle hyperkeratotic skin, anhidrotic fissuring and callus formation. Diminished arterial and venous vascular tone may lead to edema and enhanced blood flow. Diabetics with peripheral neuropathy may have a fivefold increase in arterial flow to the feet. Only a third of diabetic foot ulcers are, in fact, associated with severe arterial insufficiency. Simple bedside tests of neuropathy that can be easily conducted in the office includes such things as inability to maintain balance while standing on one foot for more than fifteen seconds (normal should be in excess of forty-five seconds).

At the bedside, clinical evaluation of vibration (with a 128 Hz tuning fork at the great toe), pinprick and light touch at the great toe with cotton wool will suffice along with deep tendon reflex evaluation. Temperature sensation over the dorsum of the foot can be added. Monofilament buckling is commonly described. One gram of linear pressure (the 4.17 Semmes-Weinstein monofilament) can be appreciated by the normally sensate foot. Loss of so-called protective sensation is claimed to be present when 10 gm of linear pressure (the 5.07 monofilament) cannot be felt. Ten percent of patients with skin breakdown, however, are capable of feeling the 5.07 monofilament.

Patients with diabetic sensory neuropathy may have diminished or absent sensation representing negative symptoms with or without associated positive symptoms. The positive symptoms more characteristic of small fiber neuropathy include dysesthesia, tingling, burning, numbness and diminished pain and temperature perception. Features more consistent with large fiber neuropathy include diminished or absent deep tendon reflexes, vibration and proprioceptive sensation.

Rapid glycemic control in type 1 or 2 diabetics started on insulin or oral agents is occasionally associated with acute onset within 2 – 4 weeks of severe burning pain and allodynia in the feet that may spread more proximally and later affect the hands and trunk. This is an axonal sensory motor neuropathy predominantly affecting sensory fibres. Symptoms gradually improve in 3 – 8 months and may resolve. Reflexes usually diminished but sensory testing may be normal. Biopsy discloses acute axonal loss affecting both myelinated and un-myelinated fibres. Proliferating new vessels with ateriovenous shunting and possible “steal effect” may lead to an ischemic endoneurium.

Diabetics with sensory neuropathy are more prone to pressure palsies (with complaint of submetatarsal and toe burning or paresthesia) against poorly fitting toe boxes. The overpronated foot, common in diabetics, leads to excessive stretching of the posterior tibial nerve in the tarsal tunnel. This is an entrapment neuropathy in the zone about the medial malleolus where a positive Tinel’s sign to nerve percussion may be elicited. Similarly, tibial nerve impingement by the top line of the shoe medial heel counter may lead to entrapment symptoms referred to the arch and plantar aspect of the foot from the medial tarsal tunnel.

Intrinsic muscles are damaged by neuropathy and heal poorly because of vasculopathy. The lateral arch drops most frequently in diabetics where there is loss of intrinsic and interosseous muscle function. The fifth metatarsal head and base drop down and rotate
externally when loaded. Furthermore, diabetics use the long peroneal muscle to drive off the first metatarsal, and have therefore an excessively down-driven plantar-flexed first ray. This can be assessed by palpating an increased pressure against the examiner’s thumbs held over the metatarsal heads, as the supine patient is instructed to plantar flex. Equinus posturing is very characteristic of diabetic neuropathy with loss of 10-degrees of dorsiflexion.

The wasted, so-called intrinsic-minus foot may have prominence of the extensor tendons coupled with claw toe deformity and restricted passive plantar flexion of the toes.

Furthermore, calluses to which diabetics are prone because of anhidrosis and increased focal pressures can further aggravate local pressure by more than 30%. Reduction of calluses by filing with foot files, pumice stone and debridement, is very important.

Of diabetics with foot ulcers, approximately two-thirds have neuropathy without vascular disease, 15-20% have vascular disease without neuropathy, while up to 20% are afflicted with both.

Protective pain sensory loss, as well as dry fissured skin from autonomic involvement and pressure from ill-fitting footwear put the diabetic at increased risk for ulceration. Small vessel disease and immunologic abnormalities make these wounds more prone to superficial and deep sepsis.

Neuropathic ulcers, by and large, tend to be painless, typically with a punched-out appearance, usually located on the sole or edge of the foot, often in conjunction with calluses and lost sensation with diminished reflexes. Veins may be dilated, the foot is often dry and warm, and may be even red in appearance. Bone deformities commonly underlie these pressure ulcers.

Ischemic or neuro-ischemic ulcers in contrast are more commonly located on the toes and the dorsa of the feet. Sensory findings are variable and calluses are often absent. Lesions tend to be more painful with absent pulses, and the feet are cooler, often pale, and sometimes even cyanosed. Weak but palpable pedal pulses, however, do not entirely rule out significant arterial obstruction more distally in diabetic patients.

Diabetic patients with end-stage renal failure on dialysis may develop uremic vascular calcifications with ulcerations related to calciphylaxis.

Magnetic spectroscopy to assess foot muscle energy shows reduced energy reserves in the foot muscles of diabetics, likely related to micro-circulatory impairment. Hyperspectral imaging to assess hemoglobin saturation shows both forearm and foot reduction in non-neuropathic diabetics compared to controls, with even further reductions in neuropathic groups. Hemoglobin concentration is therefore reduced in the skin of patients with diabetes and accentuated when the foot is neuropathic.

**PHARMACOTHERAPY AND DIABETIC NEUROPATHY:**
A detailed review of drug intervention for both prevention and treatment of symptomatic diabetic neuropathy is beyond the scope of this monograph, but the following represents a distillation of some of the latest information up to early 2012:

1. Benfotiamine is a form of high-dose thiamine used to activate the reductive pentose phosphate pathway in order to block triggers for toxic kinases and hexosamine factors, which promote microvascular complications. It is a co-factor for many enzymes. Diabetics have a relative deficiency of thiamine through increased renal clearance. Thiamine 7 - 70mg per kilogram per day and Benfotiamine 80 – 100mg per kilogram per day, both appear to reduce diabetic nephropathy, retinopathy, lipidemia and neuropathy. Peroneal nerve conduction, as well as paresthesia appear to improve with supplements of B6, B12 and Benfotiamine. Thiamine in doses of 100 – 600mg per day are likely to be used clinically and have an even greater effect on reducing triglyceride and LDL. It would be reasonable empirically in general practice to recommend B-100s, one to two tablets daily.

2. Aldose reductase inhibitors affect the polyol pathway and reduce accumulation of toxic Sorbitol in the peripheral nerve. Nerve conduction speed is enhanced by 1 – 2m per second. Currently being studied are Epalrestat, Fidarestat and Ranirestat.

3. Ruboxistaurin 32mg daily for twelve months appears to improve vibration perception with reduction in pain symptoms. It is a protein kinase C inhibitor in phase 3 clinical trials for painful diabetic neuropathy and diabetic neuropathy. (Trial has now been terminated).

4. Alpha-lipoic acid reduces oxidative stress from nitrous oxide and oxygen-free radicals. Some randomized trials suggest that 600mg per day versus placebo which is associated with a 50% reduction in pain in approximately half of patients.

5. Tricyclic antidepressants have yet to be eclipsed in terms of benefit and are a reasonable choice for mono-therapy. Small doses of amitriptyline 10 – 25mg at night for older patients and, for those sensitive to anti-cholinergic affects, nortriptyline titrated from 25mg up to 150mg is a good option. Cyclobenzaprine (Flexeril) 10mg three times daily is a TCA-like drug that must not be coadministered with tricyclics. It may be of benefit in the lightning-shooting type neuropathic pain (lancinating pain).

6. Duloxetine (Cymbalta/Yentreve – Eli Lilly. FDA approved September 2004) and venlafaxine (Effexor) exert both norepinephrine and Serotonin re-uptake inhibition. Duloxetine can be titrated from 20 to 40 to 120mg. 60mg appears to be the best tolerated dose for diabetic neuropathy. It is safe at this dose for both pain and depression. Diminished appetite and sleepiness are the main side effects and nausea in particular with doses of 120mg. Some reports suggest fewer than 40% of patients have a beneficial response, while up to 85% experience unpleasant side effects. Duloxetine has not emerged as a particularly useful antidepressant however 50% of patients with associated stress urinary incontinence (SUI) report benefit and it was for this indication that Duloxetine was introduced first in Europe.

Duloxetine should be avoided in patients with hepatic dysfunction. One study suggested an approximately 50% reduction in pain in 50% of patients, while another
suggested that the number needed to treat was 6 to find a patient with 50% pain reduction.

7. Venlafaxine appears better than other SSRIs, which may also be of benefit, but are less predictable. Treatment dosages begin at 37.5mg per day, titrated weekly by 37.5mg to maintenance dose range of 150 – 225mg per day. Sweating, nausea, sedation and hypertension are the principal adverse affects and lower doses are required with renal impairment.

8. From the standpoint of side effect tolerance (largely anticholinergic), nortriptyline is better than desipramine, which is better than amitriptyline.

9. Not more than half the patients tried with gabapentin (Neurontin) have a better than 40% response, even titrated to full doses of 3600mg per day. Slow-release Morphine appears to be better than gabapentin as mono-therapy, and equivalent to and better tolerated than antidepressants. The combination, however, of Morphine and gabapentin was recently demonstrated at Queen’s University to have a synergy leading to better pain control at lower doses of each agent, and therefore better tolerated. M-eslon 15mg bid and gabapentin 400mg qid, on the average was superior to gabapentin 2400mg as a single agent. The mean maximum tolerated dose of Morphine was 45mg per day and gabapentin 2200mg, when used as a single agent.

10. Tricyclic antidepressants, however, probably should be the drug first tried and certainly before beginning the Morphine-gabapentin combination, and studies demonstrated it requires the smallest patient numbers needed to treat.

11. Topiramate (Topamox) slowly titrated from 12.5mg per day, over six months to a total of 100mg per day, may be more effective than gabapentin and equally effective and better tolerated than rapid titration to 300mg. Topiramate may be particularly helpful in diabetics as it is often associated with a 5 – 10% drop in body weight. There is some evidence that it may change the biology of neuropathy.

12. Marijuana is now available through an application process with the Health Protection Branch in Ottawa. Its analgesic benefit in pain from neuropathy has been demonstrated in particular for multiple sclerosis. Cannabinoids act both centrally at the CB-1 receptor and peripherally at the CB-2 receptor. Synthetic Cannabinoids include dronabinal (Marinol) and nabilone (Cesamet with greater than 50% associated dizziness). The latter is a synthetic transisomer of THC. By mouth its onset is 30 – 60 minutes and lasts 4 – 6 hours, currently used most commonly for HIV anorexia and for managing nausea and vomiting with chemotherapy. Sativex is a cannabis-based pharmaceutical product being studied for peripheral neuropathic pain in Multiple Sclerosis.

13. Because predictable and impressive efficacy has not been demonstrated with any one of these agents, in general combination therapy appears to work best for neuropathic pain.

14. Anticonvulsants including Topiramate, Tegretol and Neurontin, all are claimed to have roles in treating painful neuropathy including post-herpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, phantom pain, entrapment neuropathy, Parkinson and MS-associated neuropathic pain, central and stroke-related pain and reflex sympathetic dystrophy.
15. NNT (numbers needed to treat in order to capture one patient who benefits therapeutically) show the following: TCAs are best at 1.4 if titrated to optimal dose, NMDA antagonists such as ketamine and dextromethorphan, 1.8; diphenylhydantoin (Dilantin), 2.2; Tegretol, 3.3; Tramadol (mild u-opioid receptor and NE/5H7 uptake inhibitor), 3.3; gabapentin (Neurontin), 3.7; pregabalin (Lyrica), approximately 4.5; Capsaicin, 5.0; SSRIs, 6.7.

16. Neuropathic pain management can be enhanced without side effects by the use of topical transdermal gels (e.g. PLO, PCCA-Lipoderm, Delivra) into which multiple pharmacologic agents can be compounded. This should be performed at a specialist compounding pharmacy rather than at a regular pharmacy. Medications that can be delivered this way include carbamazepine, diphenylhydantoin, gabapentin, amitriptyline, ketamine, lidocaine, benzocaine and tetracaine, etc. It is said that the addition of ketoprofen 5% or DMSO 5% can enhance penetration. L-arginine cream applied twice daily has been shown to increase Doppler flow by 33% at the metatarsal zone and 35% at the Achilles tendon with an average temperature increase of 5-degrees Fahrenheit at the metatarsal and 8-degrees at the great toe. It is postulated that the increased blood flow is generated by nitric oxide causing smooth muscle relaxation and vasodilation. Normally nitric oxide is generated in the endothelium through the oxidation of L-arginine by endothelial nitric oxide synthetase. Diabetics have abnormally low levels of L-arginine. Transdermal administration appears to improve vascular circulation and temperature of the feet of diabetic patients studied in case controlled fashion. Patients receiving a topical preparation containing both amitriptyline 50mg and ketamine 25mg reported significantly greater analgesia by days 3-7, while blood levels revealed no significant systemic absorption of either amitriptyline or ketamine. Delivra as a vehicle claims pain modifying properties.

17. Long courses of metronidazole should be avoided as metronidazole can induce peripheral neuropathy.

18. A high-potency multiple mineral and vitamin preparation as a once-a-day multivitamin is encouraged. This can be implemented following an empiric trial of high-potency B vitamins for one month, taken as B50s or B100s. In the USA by prescription only, Metanx can be prescribed, a vitamin supplement of high potency metabolites of vitamins B6, B12 and folic acid, said to be more effective and bioavailable with some studies suggesting up to 25% of symptomatic neuropathy patients reporting significant improvement. B6, however, in doses exceeding 200mg/d should be avoided as high dose B6 may be ironically neurotoxic and aggravate peripheral neuropathy symptoms.

19. In 2005, pregabalin (Lyrica) became available as a further option for oral management of neuropathy. It appears more effective and better tolerated than gabapentin. These drugs should be titrated from the lowest dose very slowly over several weeks or months as the therapeutic index is very narrow. It is currently approved (FDA, December 2004) for post-herpetic and diabetic painful neuropathy. The most commonly observed adverse events with Lyrica at twice the placebo rate include dizziness, somnolence, peripheral edema and dry mouth with reported pharmacodynamic interactions with Oxycodon, lorazepam, ethanol and thiazolidinedione oral diabetic agents. Pregabalin is excreted largely unchanged in the urine and not protein bound, therefore little potential for abnormal pharmacokinetic
interactions with other drugs. It has faster onset and can be more rapidly titrated than Neurontin. Best responses were at a full 300mg twice daily dose with NNT (numbers needed to treat) of 3 – 7 patients (average 4.5 in 10 randomized trials) for a 50% or better response that was a 3-point reduction on an 11-point numerical rating scale for pain. There is no convincing evidence yet of clear superiority of Lyrica over other treatments; however, Brill et al have reported in 2011 the results of a very comprehensive review of the neuropathic pain literature from the past several decades suggesting the superiority of pregabalin over other treatments for which randomized control trials and better quality evidence are available; however, the results are hardly spectacular.

20. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive glucose control in Type I diabetics is associated with a significant reduction in the risk for developing painful diabetic neuropathy. The frequency of neuropathy is reduced as well with tight glycemic control in Type II diabetics whose symptoms of numbness, tingling, burning and pins-and-needles may fluctuate according to blood sugar control.

**DIABETIC OSTEOARTHRPATHY (CHARCOT DISEASE):**

Also known as neuropathic arthropathy or the Charcot foot, diabetic osteoarthropathy afflicts approximately 2% of diabetics. 75% affect the mid-foot at the mid-tarsal and tarsometatarsal joints, 20% affect the hind foot, while true ankle involvement is uncommon (5%) as is MTP joint disease. Very rarely a different syndrome of progressive dissolution of metatarsal heads is seen in patients with severe neuropathy.

Charcot disease is often classified in three stages: Stage 1 – Development or destructive phase; Stage 2 – Coalescence/absorptive/replicative; Stage 3 – Regenerative, reparative and remodeling. From a practical clinical standpoint, however, it is helpful to identify the acute Charcot syndrome as atrophic, destructive, hyperemic often with a hot swollen and sometimes painful foot. The chronic late-stage syndrome is characterized by hypertrophic and sclerotic bone with a cool quiescent phase and often rigid deformed, frequently rocker bottomed foot.

Mid-tarsal collapse from dissolution of bone and joint with weakening of ligamentous supportive structures may lead to a typical rocker-bottom deformity, mid and medial plantar bumps secondary to bony subluxation, as well as loss of the medial longitudinal arch. Reversal of the anterior metatarsal arch is common. Mid and hind foot plantar ulcers have a strong correlation with the presence of Charcot arthropathy.

Although often thought to be a chronic condition, one may see both acute and subacute Charcot feet, characterized by rapid progression of collapse of the bony architecture over a period of days to weeks, with an associated painful, warm and swollen foot which is usually unilateral; although the radiography of the clinically uninvolved foot may show early neuropathic changes as well. The shape of these feet are in contra-distinction to that of the typical neuropathically denervated foot with wasted, weakened intrinsic metatarsal overload, clawed toes, cavus arch and short heel cords limiting dorsiflexion.
It is postulated that chronically high blood sugar leads to cross-linked collagen causing joints and ligaments to become stiff while weakening skin. Cross-linked myelin leads to loss of large fibers with loss of protective sensation, leading to wasting and the so-called intrinsic minus foot with diminished shear resistance, stiff ankle joints and tight heel cords, all contributing to increased forefoot pressure and tendency to breakdown in the submetatarsal zones. Microvascular disease with smoking aggravates the risk.

Tendons, tendon sheaths and joint capsules are fairly dysvascular, permitting infection to spread more quickly with more difficult treatment than osteomyelitis. There is also much less lymphatic drainage on the plantar aspect of the foot than the dorsum. Pulselessness is not an absolute contra-indication to transmetatarsal amputation, nor is infection in the deep posterior compartment or peroneal compartment. Surgery requires removal of all tendons and lengthening of the heel cord as transmetatarsal amputations shortens the lever-arm.

There are three natural rockers in the foot during gait; the heel representing the heel-strike rocker, the ankle representing the mid-stance rocker and the MTP joints representing the heel-off rocker. Restrictions in diabetics and those with a Charcot rocker foot often create a rocker across the transmetatarsal or tarsometatarsal Lisfranc joints with midfoot collapse and patients therefore may be pushing off from the midfoot rather than the ball of the foot. Forces at the ankle and midfoot are 2 – 3 times greater than those at the hip and knee.

Very uncommonly hematogenous spread of bacteria with osteomyelitis can complicate the Charcot foot. The hallmarks of infection are focal osteolysis with increased pain, high white blood count, sedimentation rate and CRP. There may be a focus of ovoid destruction with erythema that persists for more than twenty minutes with the foot resting in elevation. A white cell Indium scan or MRI with gadolinium may help identify a hidden abscess.

Bisphosphonates may help consolidation in the regenerative phase of the Charcot foot and should be tried empirically, possibly at pagetoid doses for a few months.

A dislocated Charcot joint is unstable and therefore difficult to consolidate and heal. It would be an indication for surgical stabilization. Surgical ostectomy for a stable prolapsed deformity should be considered to prevent skin breakdown.

The principal indications for surgery on a Charcot foot include an un-castable, unbraceable and un-shoeable foot. Severe malalignment with subluxation, instability, deep infections and recurrent ulcers are other indications for surgery on a chronic Charcot foot. Tobacco and alcohol consumption both contribute to Charcot and post-operative non-unions.

It is not generally recognized that the undiagnosed diabetic may first come to clinical attention with any of the following:
1. Asensate foot with trophic neuropathic indolent plantar ulcers.
2. Extensive distal vascular calcification detected either by radiography or very high ankle pressures secondary to arterial non-compressibility (paradoxically high ABI with ankle pressures often greater than 250 mm Hg).
3. Acute Charcot arthropathy mimicking osteomyelitis (osteomyelitis should only be considered if there is an open lesion on the foot).
4. Acute neuropathic symptoms of burning or paresthesia.
5. Pressure palsy and entrapment neuropathy.

**DIABETIC FOOT INFECTIONS:**

Close to 90% of foot amputations follow an infection usually complicating an open wound or sinus. Pure ischemia is a relatively uncommon predisposing cause for amputation in diabetics but it is the most important determinant of the level of choice at which an amputation should be performed.

Staphylococcus and Streptococcus are the most common pathogens in superficial infections in diabetics as well as non-diabetics. Cellulitis is usually mono-bacterial. Superficial wounds, however, average two bacterial species, while deep limb-threatening infections often four or more species.

Chronic diabetic foot ulcers typically are polymicrobial including anaerobic gram positive cocci, staphylococcus, peptoniphilus, rhodopseudomonas, enterococcus, Veillonella, clostridium, finegaldia. This is in contrast to non-diabetic chronic venous ulcers which typically have gram-negative rods, enterobacter, Serratia and Proteus. Bacteroides, Fusobacteria, peptococcus and Peptostreptococcus may also be seen.

Deep diabetic foot infections, however, are typically Staph and Strep when very acute and polymicrobial when more chronic. One large recent study noted the following organisms complicating deep diabetic foot infections: approximately 45% Staph aureus, 35% Streptococcus, 29% enterococcus, 26% Staph epidermidis, 22% Peptostreptococcus, 19% diptheroids, 16% pseudomonas. Pseudomonas should be suspected and covered for in all wounds caused by penetrating objects such as nails and screws through the soles of sneakers. MRI is quite sensitive and specific for detection of osteomyelitis and deep soft-tissue infections which can spread rapidly along deep fascial planes.

Chronic draining sinus tracts as well as deep penetrating ulcers very often have associated chronic osteomyelitis and so should both be probed as well as cultured from the depths with a penetrating swab. A specimen of bone taken by scraping or biopsy yields the most accurate results to direct long term antibiotic management. Extensive surgical debridement of the bone should be undertaken if there are deep erosive bony lesions.
If a sterile probe hits bone, there should be a presumptive diagnosis of osteomyelitis which will obviate the need for nuclear bone scanning. Technesium bone scanning is positive in both, while Gallium scanning is often unhelpful in differentiating osteomyelitis from Charcot arthropathy. Scanning need not be performed if there is no ulceration as osteomyelitis of the foot is almost never hematogenous. If ulceration is present and the diagnosis in doubt, MR scanning with Gadolinium is the most sensitive test for the diagnosis of tarsal osteomyelitis, but unfortunately not yet readily available widely. Caution is advised with diabetics in chronic renal failure, 5% of who develop nephrogenic fibrosing dermopathy following intravenous Gadolinium exposure (thick, bound, indurated, pigmented skin with bound and contractured joints). Ischemia, however, often decreases inflammatory signs and chronic diabetic ulcers may not have much in the way of white blood cell migration and pus. A sedimentation rate in excess of 40 carries a 12 times likelihood of associated osteomyelitis.

Enterococcus is especially important in diabetic osteomyelitis, while anaerobes which characterize diabetic wounds are grown largely only in deep polymicrobial infections. Deep forefoot intermetatarsal and fascial sepsis is best evaluated with urgent forefoot CT scanning.

It is helpful to bring the nose close to a wound and sniff deeply. A strong, deep pungent odour or putrid discharge, is characteristic of polymicrobial anaerobic infections and warrants oral or intravenous antibiotic therapy. A shallow, clean-appearing wound that has a very mild malodour, probably represents colonization with some microbial contamination and low-grade subclinical infection that warrants topical treatment. Iodine-containing paste such as Cadexomer iodide and the use of topical benzoyl peroxide up to 8%, and topical clindamycin or metronidazole gel can be helpful. Clindoxyl, currently advocated for acne, contains 1% clindamycin with 5% benzoyl peroxide and is handy for topical management of contaminated and colonized but not obviously infected wounds. It can be used as an adjunct with oral therapy for more serious infections. Silver sulfadiazine (Flamazine cream) reduces bacterial contamination while at the same time is angiogenic and promotes granulation better than all other topical agents. Iodosorb should not be used for long periods of time, in order to avoid toxic thyroid effects from iodine absorption. (Hypo- or Hyper-thyroidism).

Chronic poorly healing diabetic wounds may be stalled because of superficial infection which may be inapparent. This represents excessive or critical colonization. These wounds may be characterized by non-healing, increased exudate, red and bleeding, smelly and with debris. These wounds should be treated aggressively with topical antiseptics that include chlorhexidine (Baxedin), sodium hypochlorite (Deacon's solution), Proviodine, Tea Tree Oil and hydrogen peroxide. Following soaks and scrubs with these antiseptics, topical antimicrobial agents can include any number of iodine or silver containing products. Every effort should be made to mechanically reduce and eliminate biofilms which house bacterial cells in a structured mass enclosed in a self-produced polysaccharide matrix which adheres to the wound surface and through which antibiotics may simply not penetrate.
Deeper infections require systemic antibiotics and are characterized by greater size, warmth (greater than 3-degree Fahrenheit difference from other surrounding tissues), probing to bone, increasing exudate, malodour and friable or exuberant granulation tissue.

Antibiotic therapy may be directed by microbial culture, best performed by curettage of the base of a wound (including exposed bone) after topical cleansing and gauze debridement. Twirling a sterile Q-tip swab vigorously after superficially cleansing a wound is a reasonable non-invasive way of acquiring reasonably accurate cultures. Curettage with a sharp disposable curette is an easy and excellent way to acquire tissue for culture and sensitivity. Empiric therapy for deep and open foot infections includes monotherapy with clindamycin. Patients should be warned to report diarrhea immediately as clindamycin is more apt than other antibiotics to trigger antibiotic associated diarrhea and severe pseudo-membranous colitis. Empiric combination therapy should cover Staph, Strep and anaerobes, and may include such combinations as Metronidazole plus any of Co-trimoxazole, cloxacillin or Cephalosporin. Localized bone involvement in the toes can almost always be managed with oral antibiotics, frequently requiring long courses of 8-12 weeks.

Certain oral antibiotics are said to have close to 99% oral bioavailability and there approach equivalence with intravenous therapy. These include levoquin, moxifloxacin and the amoxicillin/clavulanic acid combination.

Patients requiring hospitalization for severely infected wounds or deep space infections may be treated empirically with intravenous Imipenem or Meropenem through a PICC line. Ertapenem (Ivanz, Merck Frost) has been approved for diabetic foot infections typically 1gm IV q24h. Piperacillin and tazobactam (Tazocin – Wyeth) I.V. for 4 – 8 weeks followed by 4 – 8 weeks of a Quinolone or Clavulin 875mg po bid is another example of a representative option.

Outpatient empiric monotherapy with Quinolones in the pre-MRSA era had been excellent but these should be avoided in patients on Amiodarone or Sotalol, in view of the potential of increasing the QT interval and precipitating torsades de pointes. Moxifloxacin and Levoquin have a broader range of anti-anaerobic coverage than does ciprofloxacin and does not require any adjustment in dose for age, renal failure or moderate liver failure. Ciprofloxacin, however, has some anti-pseudomonal activity, as does topical acetic acid 1 – 5% and this combination can be used in ulcers that are culture positive for pseudomonas or distinctly coloured green in the wound base slough. For MRSA coverage, combination therapy is now advisable.

Increasingly emerging resistance and complicated infections require newer agents, many of which are not readily available. Resistance by MRSA and pseudomonas to ciprofloxacin has been seen and in certain jurisdictions 20% of staphylococcus (MSSA) is resistant to Vancomycin, a drug in particular easy to use in renal failure patients who can take 500mg intravenously following each dialysis. Nafcillin by PICC-line pump is particularly good for MSSA. Since resistance of Staph Aureus to fluoroquinolones is
common and develops quickly and the vast majority of MRSA isolates are resistant, mono-therapy with fluoroquinolones for Staph aureus infections is not currently recommended.

In 2000, the USA – FDA approved a novel first agent in the oxazolidinone class of antibiotics marketed in the USA under the trade name of Zyvox (linezolid by Pfizer, Inc.). This drug is at least as effective in diabetic wound infections as standard treatments with aminopenicillins or betalactamase inhibitors. Linezolid out-performed aminopenicillins in patients with infected diabetic ulcers. It was equivalent for cellulitis and osteomyelitis. Linezolid 600mg q12h IV or PO, out-performed Vancomycin 1gm IV q12h, 87% versus 67% re clinical outcomes in the management of cellulitis, abscesses, infected ulcers and burns in patients contaminated with methycillin-resistant staphylococcus aureus (MRSA) infections. It has a particularly important role now that Vancomycin-resistant infections are emerging to both Staph and enterococcus (MRSA and VRE). It is 100% bio-available by mouth with side effects that commonly includes diarrhea and, in patients with renal failure, thrombocytopenia. Serotonin syndrome may occur with coadministration with SSRI. It is particularly indicated for skin and soft tissue infections with or without MRSA. This drug is toxic to mitochondria and therefore may cause lactic acidosis or peripheral neuropathy. Co-treatment with co-enzyme Q10 would be reasonable. Linezolid is anti-tuberculous but has no affect on gram-negative bacteria and some resistance to Staph aureus has been reported. New anti-MRSA tetracyclines are coming to market. The availability as an oral agent makes it particularly advantageous. Tigecyclin (a tetracycline-doxycyclin like drug) is a static drug for MRSA and VRA with a very large antimicrobial spectrum including acinetobacter. It has no pseudomonas coverage and may cause photosensitivity and vomiting.

Daptomycin (Cubicin) is a lipopeptide antibiotic administered intravenous only once every 24 hours indicated strictly for complicated skin and skin structure infections (cSSSI) with streptococcus, staphylococcus (MSSA and MRSA) and Vancomycin susceptible enterococcus. It is very rapidly cidal with very low MICs and in vitro 99% of all staphylococcus are sensitive. It may however cause neuropathy and rhabdomyolysis.

Some experts suggest that there is limited or no evidence that linezolid or daptomycin are superior to doxycycline, clindamycin or trimethoprim sulfamethoxazole in the management of soft tissue infections. It is suggested that these drugs be considered only when Staphylococcus aureus is found to be resistant to other agents, or the patient is intolerant of other agents.

Telavancin (Vibativ) is a lipoglycopeptide antibiotic administered intravenously for cSSSI with indications identical to that of daptomycin (Cubicin). It has a huge spectrum of coverage, particularly gram positive, but should be avoided in the long Qt patient.

Mono-therapy with oral regimen for mild skin and soft tissue infections in diabetics (small, superficial, painless) could start with cephalexin 500mg po qid OR clindamycin 300mg po tid (covers MRSA) OR amoxicillin/clavulanate 875mg po bid.
For moderate or severe skin and soft tissue infections ertapenem 1gm IV q24h OR ciprofloxacin 500mg po bid/400mg IV q12h plus either clindamycin 600mg IV q8h/300mg – 450mg po tid OR Metronidazole 500mg IV/po tid. If at risk for MRSA, substitute Vancomycin for clindamycin. Piperacillin/tazobactam 4.5gm IV q6h or ciprofloxacin 400mg IV q12h plus clindamycin 600mg IV q8h are another option. For those at risk for community acquired MRSA, Pip/tazo plus Vancomycin OR intravenous ciprofloxacin 400mg IV q12h plus Metronidazole 500mg IV q8h plus Vancomycin. Avoid quinolones in patients who were on them as outpatients.

Diabetics are more prone to necrotizing fasciitis, typically deep, painful and rapidly progressive requiring urgent debridement and I.V antibiotics with hospitalization. Palpable crepitus and gas on plain x-ray implies gas producing bacteria (E.coli, clostridial myonecrosis) and warrants surgery with adjunctive antibiotics – Vancomycin PLUS Pip/tazo OR cefepine PLUS clindamycin. If penicillin allergic, Vancomycin PLUS Cipro I.V. PLUS clindamycin I.V. For confirmed hemolytic streptococci: penicillin G-24 million units PLUS clindamycin 600 -900 mgm I.V. Q8h.

**FOOT MANAGEMENT:**

1. The presence of hypertension, hyperlipidemia and smoking add vastly to the diabetic’s risk of peripheral vascular disease and should be treated aggressively.

2. Dry skin, which is almost ubiquitous and may be associated with micro-fissures, should be managed by avoiding excessive bathing, avoidance of detergent soaps in favour of non-detergent skin cleansers and twice daily applications of moisturizers (such as those that are lanolin and urea based). Petroleum jelly or petroleum-based moisturizers may be used at night after bathing and covered with cotton socks to retain moisture and soften callosities.

3. Corns and calluses should be reduced regularly by the patient or caregiver with the use of pumice stones and files, supplemented as necessary by the clinician with debridement.

4. An easy way for diabetics and their caregivers to handle difficult and onychogryphotic nails, is to permit them in fact to grow out at least 2 mm beyond the nail bed, maintained smooth by weekly filing with a large emery board rather than trimming with clippers.

5. Ingrown nails should be treated temporarily by wedge resections and debridement of the sulci; and, permanently by partial or complete resection with ablation of the matrix.

6. For patients with poor hygiene, thrice weekly soaks for 10 minutes in lukewarm water with triclosan and oiled products with gentle face cloth cleansing between the toes, leads to a reduction in fungal, yeast and bacterial proliferation.

7. Web space fissures and maceration can be treated with anti-fungal and anti-yeast creams along with toe separators. Silicone gel and foam toe separators may be effectively used in the first web space, particularly if there is hallux valgus, while lesser toes are best separated with lamb’s wool which permits air circulation and drying without compressing toe tissues. Carded merino lamb’s wool roving is best.
This is often the portal of entry for cellulitis, recurrent leg cellulitis and cellulitis complicating lymphedema.

8. Most patients and their caregivers can be taught daily foot surveillance and self care of their feet. Those with visual disturbance, arthritis, cognitive impairment, ulcerated lesions, multiple risk factors and other obstacles to self care, should be followed regularly by an appropriately skilled clinician. These may include nail care nurses, chiropodists, podiatrists, primary care physicians and surgical and medical specialists.

9. Attention to specialty footwear and insoles should be part of the prophylactic management of every diabetic’s feet, as well as those with clinical problems. Underlying the majority of neuropathic and vascular ulcers, ingrown toenails, corns and calluses, is a conflict between foot and footwear. Professional pedorthic management, although frequently neglected, in fact represents the most important contribution to diabetic foot care management.

**DIABETIC ULCERS:**

The majority of diabetic ulcers are located on the feet. Although traditionally these are often thought to be neuropathic ulcers (mal perforans) most should be recognized for what they are, which are pressure and shearing ulcers, often secondary to conflict with ill-fitting footwear. The most critical element of long term management and prevention is biomechanical offloading and protection with expert pedorthic care and proper footwear with modifications. Even most ischemic ulcers begin with trauma or pressure as a final inciting or contributing element. Ulcers unrelated to pressure or trauma includes necrobiosis lipoidica diabeticorum which are most often pre-tibial but may ulcerate on occasion. Biopsy may be required to facilitate the diagnosis. An uncommon condition is that of idiopathic bullae of diabetes (Bullosa Diabeticorum) more common in males and frequently associated with neuropathy. They may ulcerate and present as full thickness blisters to the dermal margin. They typically do not scar. They may appear pustular and occasionally bloody. They occur at the dermal-epidermal junction. Secondary staphylococcal infection may occur. The bullae should be left intact. Those that are open heal rapidly with oral cephalosporin.

Diabetic foot ulcer recurrent rates are 45% one year, 60% two year and 70% by five years.

The principles of diabetic wound management are complex requiring multidisciplinary management, as well as a multifactorial approach that includes attention to the following:

1. Necrotic tissue as well as heaped up hyperkeratosis should be sharply debrided as widely and deeply as possible. Exuberant granulation tissue as well as gray sloughy base and any exposed bone should be aggressively debrided and resected as otherwise the wounds may remain stagnant.

2. Low grade infection or bacterial colonization can be treated topically with such agents as iodine-containing paste (Iodosorb); silver sulfadiazine cream (SSD, Flamazine); silver containing gels (Silvasorb) or powder (Arglaes); silver impregnated foam (Mepilex Ag); Calcium Alginate with silver; silver impregnated
mesh (Silverlon and Acticoat, metallic silver topical wound dressings capable of delivering ionic silver to the wound surface in concentrations required to kill microbes including MRSA and VRE, but at considerably lower levels than is cytotoxic to wound-healing); fucidic acid or mupirocin ointment, as well as over-the-counter topical antibiotic ointments. Smelly wounds can be treated with topical metronidazole gel (Metrogel) or clindamycin 1% with benzoyl peroxide 5% (Clindoxyl, Benzaclin).

3. Bony prominences should be decompressed by the use of extra-depth, extra-width toe box footwear, broad straight-lasted footwear, footwear with Lycra-like extendable toe boxes and soft-lined open-toed arch supporting sandals.

4. Small and large vessel circulation should be maintained or improved with such agents as ASA, clopidogrel, pentoxifylline, topical Nitroglycerine cream and reduction or elimination of co-administered Beta Blockers.

5. Nutritional supplementation to facilitate wound healing, which may include co-factors such as vitamin C, zinc and copper, readily available over the counter. Diabetic ulcers are often deficient in magnesium, calcium, zinc, vitamin A, riboflavin and folic acid. High doses of omega-3 fatty acid supplements are thought to reduce peri-wound thrombosis, inflammation and cell-proliferation.

6. Wounds, by and large, should remain moist to facilitate angiogenesis, fibrocyte migration and epithelialization.

7. Impediments to wound healing should be eliminated, such as undue pressure against footwear, mattresses and bed clothing, excessive maceration from wound care products and contact inhibition by exposed bone.

8. Plantar ulcers may be managed with the assistance of total contact plaster casting or removable light plastic rigid rocker-soled soft-lined air cast walker with modified foam or Plastizote liner as an instant total contact device (currently used in fewer than 30% of patients with plantar ulcers). Note that the small Air Cast walker is not rockered and should not be used with diabetic foot ulcers. The Darco Body Armour rigid walking boot currently represents amongst the most aggressive and durable supportive offloading boots available. Short boots are adequate for forefoot offloading while hindfoot offloading is somewhat better with high boots where weight-bearing can be transferred to some extent to the lower leg and calf.

9. Compounding pharmacists can create transdermal gels with lipoderm or pluronic lethicine organo-gels, into which a mixture of pharmacologic agents can be added to promote wound healing and these include diphenylhydantoin 5% and misoprostol 0.0024%. Topical mixtures of 5% benzocaine/lidocaine and tetracaine can help with pain control, while circulation around the wound can be enhanced with topical gels containing nitroglycerin, nifedipine and pentoxifylline. Topical insulin may facilitate wound healing (40 units of insulin per ml).

10. Although there has been much enthusiasm for cytokine growth factors, these have not, as yet, proven themselves to be highly effective nor worth the extraordinary cost. These include platelet-derived growth factor (Regranex), epidermal growth factor, angiogenesis factor, transforming growth factor, fibroblastic growth factor, interleukin I and tumour necrosis factor. Similarly, new technologies of artificial "skin" such as bovine collagen containing living human fibroblasts (Apligraf) and...
living, human fibroblasts derived dermis (Dermagraft) have not proven practical, although when properly used improve both healing rates and times. These are sometimes referred to as metabolically active human dermal replacement for the treatment of foot ulcers. Advanced wound healing centres may utilize products for whom there is support in randomized clinic trial meta analyses and these include for diabetic ulcers: Oasis, Dermagraft, Apligraf, hyperbaric oxygen, negative pressure wound treatment and topical platelet derived growth factor (Regranex).

11. Currently under investigation is E-Matrix by Encelle, which is a porcine collagen-derived biopolymer designed to mimic the extra-cellular matrix found in fetal development. It is injected underneath and around the wound. It can be used in conjunction with living skin equivalents and growth factors. It appears to work best in larger wounds greater than 2cm squared, and those which are chronic, providing twice the wound healing at 12-weeks compared to a control group. The stated rationale is to encourage wounds to heal with a more organized collagen structure that may reduce scarring and lessen the potential for recurrent ulceration.

12. Hyperbaric oxygen treatment (HBOT): Scientific studies suggest various benefits from hyperbaric oxygen including 40% increase in VEGF (vascular endothelial growth factor) after five days, 50% increase in neovascular density by ten weeks, mobilization of CD-34 bone marrow stem cells to promote wound healing following twenty treatments, enhanced fibroblast proliferation along with cytokine and growth factors such as PDGF, EGF, VEGF and TGF. In general collagen synthesis and cross linkages are improved along with angiogenesis, leukocyte killing and epithelialization. The affect of clindamycin, penicillin, sulfonamides, rifampin and immunoglycocides are potentiated with HBOT. Eighteen studies, including six randomized controlled trials suggest beneficial effects of hyperbaric oxygen therapy for ischemic ulcers and gangrene with one recent negative study, although access to this modality is currently severely restrictive and therefore often not practical. It can only be considered an adjunctive treatment. For inclusion patients must have a positive TcP02 response to 100% oxygen at one atmosphere pressure. 75% of patients improve within six weeks with thirty treatments of 90 minutes. Typical treatment is at 2.4 atmospheres with 100% oxygen. Assessment for candidacy under the aegis of Ontario Wound Care Inc. and the Judy Dan Wound Clinic, 555 Finch Avenue West, Toronto. Tel: 416-223-6600. Fax: 416-223-6764. Contact Dr. Ron Linden e-mail: drlinden@ontariowoundcare.com

13. The Circulator Boot is a diastolic counter pulsation boot that may have a role for limb salvage in the end-stage ischemic foot. Compression of the foot and leg during diastole serves to improve tissue perfusion and healing. (Most research from Bryn Mawr with one positive study from Mayo).

14. MIRE (Monochromatic Near Infra-Red Energy) is one of many available modalities of light or photonic therapy. Flexible pads contact the diabetic foot for 30 minutes, 2 – 4 times per day, in an effort to improve foot circulation for wound-healing via vasodilation of small vessels (Anodyne therapy 1-800-521-6664).

15. Adjunct low-intensity ultrasound has been used for electrically modulating the healing process of bone, which has its own piezoelectric behaviour. Ultrasound transmits micromechanical forces and strains to a fracture site and promotes bone formation in a manner consistent with the Wolff’s Law postulates. Low-intensity
ultrasound used in bone healing and re-modeling produces no heat in comparison with the high power of conventional ultrasound therapy. Animal models show accelerated healing with increased strength and stiffness of the fracture callus. Pulsed low-intensity ultrasound affects cellular function increasing calcium uptake and modulating adenylate cyclase activity, transforming growth factor beta synthesis and parathyroid hormone response. There may be a role for low intensity ultrasound as an adjunct to rest and biomechanical support in the management of fracture and non-union in diabetics and Charcot neuro-osteoarthropathy. In diabetics small fiber loss leads to sympathetic denervation with associated increase in bone blood flow that is thought to increase trabecular resorption by osteoblasts, leading to osteopenia and increased bone fragility. This is thought to be the prelude to the first stage of Charcot osteoarthropathy prior to more overt fragmentation. Increased uptake on a nuclear bone scan correlates with increasing osteoblastic activity even before the x-ray changes of more characteristic fragmentation occur. Synovial fluid and synovial biopsy in the early Charcot joint shows tiny fragments of bone and cartilagenous debris early on, which is pathognomonic. (Exogen-Smith and Nephew).

16. Negative pressure wound therapy for deep plantar and dorsal ulcers as well as after partial diabetic foot amputation (utilizing vacuum-assisted closure – VAC Therapy System) in selected patients seems to be a safe and effective treatment for complex diabetic foot wounds. A higher proportion of wounds appear to heal with this modality with faster rates and no increase in the severity of complicating infections.

17. For patients with MRSA contaminated or infected wounds, utilize a standard decolonization protocol of chlorhexidine soaks daily for bathing with the application topically of chlorhexidine 0.05% solution, both for 10-days. Silver-containing topical products can be added. Mupirocin 2% (Bactroban) 2 – 3 times daily on open wounds. Wounds that are clinically infected with MRSA should be treated with standard decolonization protocol plus 7-days of combination oral treatment with two of the following agents: Rifampin 600mg daily, Doxycycline 100mg bid, fucidic acid 500mg tid, Trimethoprim-Sulfa DS one tablet bid. Intravenous Vancomycin would be restricted for wound infections with systemic manifestations or in conjunction with MRSA-positive sputum or urine.

18. Easily friable or bleeding tissue, friable granulation tissue, stalled healing, periwound edema, new or increasing pain, may all be signs of occult wound infection or heavy colonization warranting antimicrobial therapy.

19. Monofloral Canadian honeys from buckwheat, manuka and leptospermium honeys and honey impregnated alginates have anti-staphylococcal and MRSA activity and some anti-VRE activity. (Medihoney Wound Dressing – Derma Sciences).

20. Ibuprofen releasing polymethane foams for painful ulcers (Coloplast Biatain-Ibu).

21. Protein Kinase C modulators (activators and inhibitors) have been used in Israel to effectively heal diabetic ulcers (Healor product H0/03/03).

22. The addition of erythropoietin may permit refractory diabetic ulcers to heal in patients with anemia and chronic renal failure.

23. Cell biologists at the University of California – Riverside, have demonstrated enhanced wound healing (in animal models and human in-vitro cell studies) of topically applied insulin. Topical insulin had a beneficial affect on keratinocytes (the cells that regenerate the epidermis after wounding) and on microvascular endothelial
cells (the cells that restore blood flow), presumably by switching on a number of cellular signaling proteins.

**PEDORTHIC MANAGEMENT:**

Skilled professional footwear fitting, footwear modification and manufacture of insole orthoses are best accomplished by a pedorthist. At risk patients require professional attention and should not be fitted in regular shoe stores. Management of those with more complex wounds, Charcot deformity, etc. often require materials and hands-on skills beyond that available by most primary foot care providers. Furthermore, well skilled pedorthic centers are usually the only setting in which appropriate orthopedic footwear, shoe modification and orthosis manufacture can be coordinated at one site and suitably matched.

Diabetics with neuropathy, hallux valgus and overpronation typically require an extra-width toe box, while those with overriding toes, cavus foot or claw toes require extra-depth footwear. Toe boxes with soft supple leathers or Lycra-like materials are best. Insoles are best made from dual density materials, full length and lined with a soft material such as Poron or Plastizote.

For diabetics with mobile claw toes (which can be corrected by metatarsal insole pad which straightens the toes and therefore lengthens the foot), a rocker bar on the sole or rocker modification may be safer in that it does not compromise the foot in a more cramped toe box. Toe boxes of soft leather or thermomoldable materials can be totally or point stretched as required to decompress bony prominences.

A variety of forefoot and hindfoot pressure ulcer offloading walking and wound care shoes and boots are currently available. Rigid, aggressively rockered, cast-like walking boots are available off-the-shelf, while for complex wounds and Charcot feet, custom-made long and short weight-bearing devices are available. These include the CROW (Charcot Restraint Orthopedic Walker) and custom gauntlet leg-ankle-foot orthoses (Arizona AFO).

Submetatarsal excavation along with proximal medial posting to support the metatarsal shaft may be required in the excessively plantar-flexed first ray, discussed earlier. In the neuropathic patient at risk for an impending Charcot collapse, protected weight bearing with a total contact orthoses in an orthopedic shoe is required. Those with established Charcot rocker feet and a medial arch collapse can be managed in custom-made footwear or shoes split with a modified sole to accommodate the abnormal architecture. Wide-soled orthopedic walking shoes and running shoes with medial arch buttresses and rigid rocker soles, play an important role in diabetic foot care, not only when established disease has already presented, but to prophylact all at risk patients.

Every diabetic patient, regardless of symptomatology and clinical findings, should be fit by a professional shoe-fitter. The vast majority of diabetic foot problems and
complications can be effectively prevented or treated with attention to these straightforward principles of lower extremity management.

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