The background features abstract, overlapping green geometric shapes in various shades, creating a modern and professional look. The shapes are primarily triangles and polygons, some with gradients, set against a white background.

# *Diabetic foot ulcer*

## *Approach and Management*

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# Who is at High Risk of Developing a Foot Ulcer?

- ▶ Peripheral neuropathy
- ▶ Previous ulceration or amputation
- ▶ Structural deformity or limited joint mobility
- ▶ Peripheral arterial disease
- ▶ Microvascular complications
- ▶ Elevated A1C

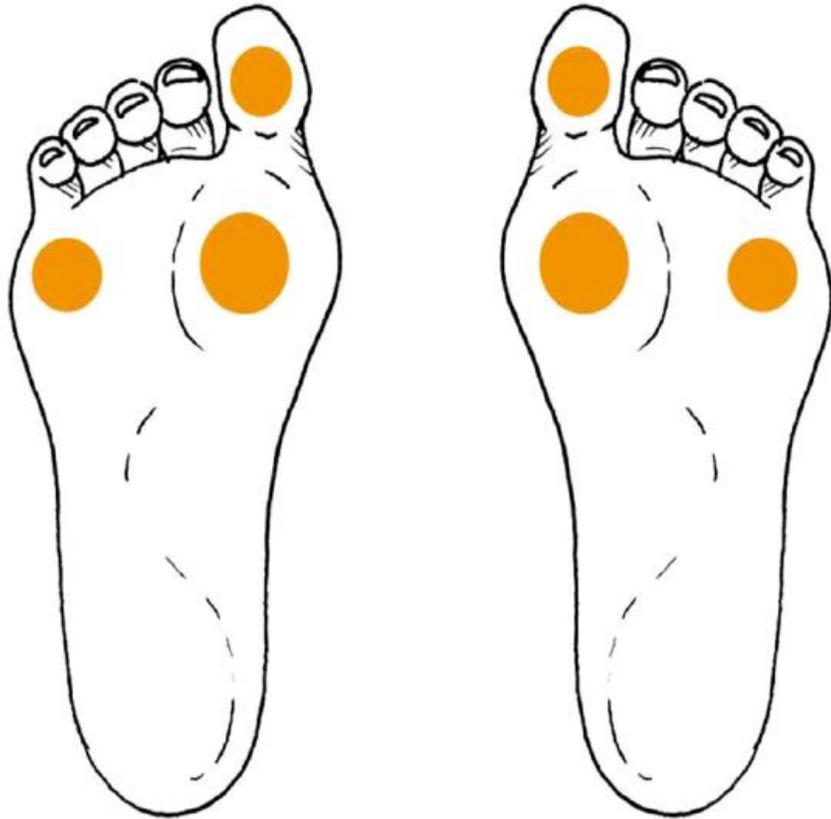
# Key Elements of the Lower Extremity Physical Examination

Element	Parameter
Inspection	<ul style="list-style-type: none"><li>• Gait</li><li>• Foot morphology (Charcot arthropathy, bony prominences)</li><li>• Toe morphology (clawtoe, hammertoe, number of toes)</li><li>• Skin: blisters, abrasions, calluses, subkeratotic hematomas or hemorrhage, ulcers, absence of hair, toe nail problems, edema, abnormal color</li><li>• Status of nails</li><li>• Foot hygiene (cleanliness, tinea pedis)</li></ul>
Palpation	<ul style="list-style-type: none"><li>• Pedal pulses</li><li>• Temperature (increased or decreased warmth)</li></ul>
Protective sensation	<ul style="list-style-type: none"><li>• Sensation to 10 gram monofilament</li></ul>
Footwear	<ul style="list-style-type: none"><li>• Exterior: signs of wear, penetrating objects</li><li>• Interior: signs of wear, foreign bodies</li></ul>

# How to Perform Proper Foot Examination

Structural Abnormalities		<ul style="list-style-type: none"><li>• Skin changes</li><li>• Evidence of infection</li><li>• Callous or ulcer</li><li>• Range of motion</li><li>• Charcot foot</li></ul>
Peripheral Arterial Assessment		<ul style="list-style-type: none"><li>• Temperature</li><li>• Skin changes</li><li>• Ankle Brachial Index</li></ul>
Neuropathy Assessment		<ul style="list-style-type: none"><li>• 10 gram monofilament</li><li>• Vibration</li><li>• Ankle Reflexes</li></ul>

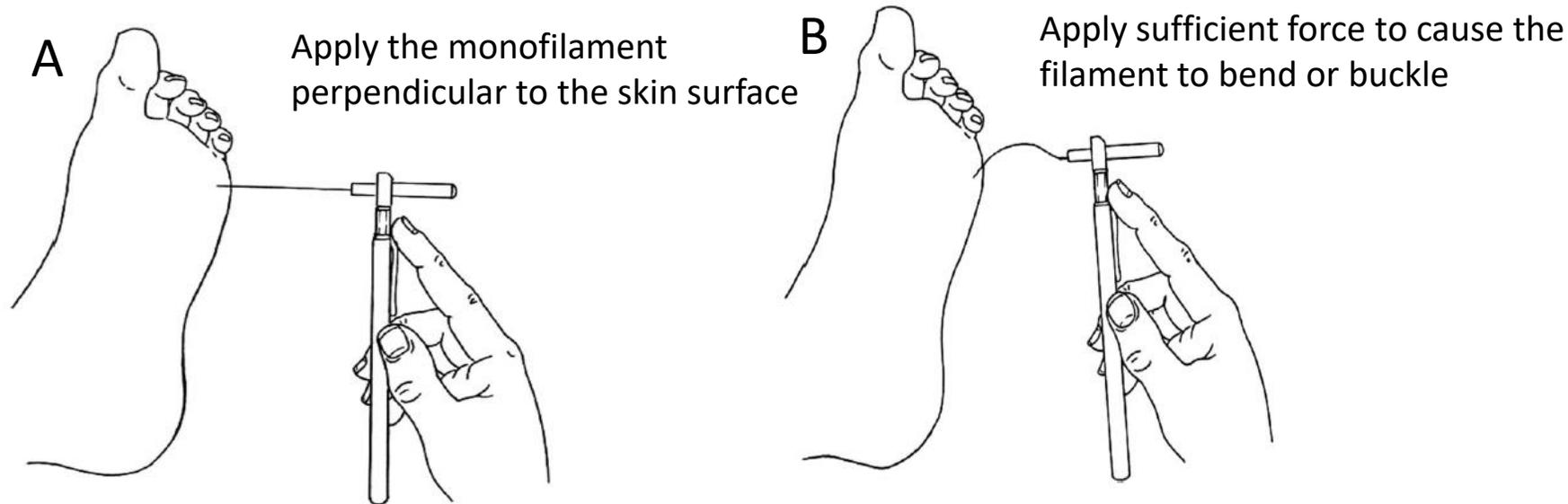
# Screening for Protective Sensation Using The 10 gram Monofilament



## How to perform the sensory examination:

- Conduct in a quiet and relaxed setting.
- Begin by applying the monofilament to the hands, elbow or forehead so that patient what to expect.
- Test the three sites on both feet shown in the figure.

# Screening for Protective Sensation Using The 10 gram Monofilament



## How to Apply the monofilament:

- Repeat the application twice at the same site, but alternate the application with at least one 'mock' application in which no filament is applied (total three questions per site)
- Protective sensation is present at each site if the patient correctly answers two out of three applications. Incorrect answers – the patient is then considered to lack protective sensation and is at risk of foot ulceration.

## DO ...

Check your feet **every day** for cuts, cracks, bruises, blisters, sores, infections, unusual markings

Use a **mirror** to see the bottom of your feet if you can not lift them up

Check the **colour** of your legs & feet – seek help if there is swelling, warmth or redness

**Wash and dry your feet every day**, especially between the toes

Apply a good **skin lotion every day** on your heels and soles. Wipe off excess

**Change your socks every day**

Trim your **nails straight across**

Clean a cut or scratch with **mild soap and water** and **cover** with dry dressing

Wear good supportive shoes or professionally fitted shoes with low heels (under 5cm)

Buy shoes in the late afternoon since your feet swell by then

Avoid extreme cold and heat (including the sun)

See a foot care specialist if you need advice or treatment

## DO NOT ...

Cut your own **corns** or **callouses**, nor treat your own **in-growing toenails** or **slivers** with a **razor or scissors**. See your doctor or foot care specialist

Use over-the-counter medications to treat corns and warts

**Apply heat** with a hot water bottle or electric blanket – may cause burns unknowingly

**Soak** your feet or use **lotion between your toes**

Take very **hot baths**

Walk **barefoot** inside or outside

Wear **tight socks, garter or elastics or knee highs**

Wear over-the-counter insoles – may cause blisters if not right for your feet

Sit for long periods of time

**Smoke**

# When Should a Foot Exam be Performed?

Low Risk		Annually
High risk for ulcer		More frequent Every 3-6 months
Foot ulcer present		Refer to an interprofessional team with expertise in foot ulcers

# University of Texas Diabetic Wound Classification System

Stage	Grade			
	0	I	II	III
<b>A (no infection or ischemia)</b>	Pre- or post-ulcerative lesion completely epithelialized	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
<b>B</b>	Infection	Infection	Infection	Infection
<b>C</b>	Ischemia	Ischemia	Ischemia	Ischemia
<b>D</b>	Infection and ischemia	Infection and ischemia	Infection and ischemia	Infection and ischemia

## Non infected

- ▶ **Superficial** diabetic foot ulcers ( grade 1; stage A) can be debrided in the clinic or at the bedside
- ▶ For **noninfected** ulcers that extend to **deeper tissues** (grade/stage: 2A, 3A) initial surgical debridement in an operating room setting
- ▶ For **pressure-related** ulcers, mechanical offloading should be implemented

## Superficial diabetic foot ulcer



## Full thickness diabetic foot ulcer



Foot from a diabetic patient with a penetrating neuropathic ulcer that is not associated with abscess formation or bone involvement.

# *Infected ulcer*

- ▶ Treatment of **infected** ( grades 1 to 3; stage B) diabetic foot ulcers:
  - Antimicrobial therapy and surgical debridement
  - The antibiotics chosen and duration of therapy depend upon the depth and severity of infection
  - Consultation with a **surgeon** is important for any infection that extends beyond the dermis

# *Ischemic Ulcer*

- ▶ Approximately **one-half** of patients with diabetic foot ulcers have ischemia (grades 1 to 3; stage C)
- ▶ In addition to proper local care (debridement, wound coverage, relief of pressure), patients with significant limb ischemia should be referred to **revascularization**
- ▶ Revascularization should be considered in patients with any degree of limb ischemia and foot ulcer that does not improve

# Combined infection and ischemia

- ▶ Infected and ischemic ulcers (grades 1 to 3; stage D)
  - Highest risk for nonhealing and amputation
  - Generally require team management
  - Medical and surgical control of infection and revascularization

Deep diabetic foot ulcer involving bone



Infected and ischemic diabetic foot ulcer



# ***MECHANICAL OFFLOADING***

# Management of diabetic foot ulcer

- ▶ Any ulcer with pressure and stress (ie, pressure-related heel ulcers or medial/lateral foot ulcers) or repetitive moderate pressure (plantar foot ulcers) will benefit from **pressure reduction**
- total contact casts
- cast walkers
- wedge shoes
- bed rest

# Total contact cast

- ▶ A total contact cast is a padded fiberglass or plaster shell designed to take pressure off the heel or elsewhere on the foot
- ▶ Patients with a total contact cast also had faster healing
- ❑ **Disadvantages**
  - ▶ Inability to inspect the foot frequently,
  - ▶ Inconvenience in activities of daily living
  - ▶ Risk of developing a secondary ulcer particularly in patients with neuropathy

# Total contact cast

## Contraindications

- Infected ulcers or wounds
- Osteomyelitis
- Peripheral ischemia (ankle-brachial index  $<0.6$ )
- Bilateral ulceration
- Lower extremity amputation
- Heel ulceration

# Total contact cast



## ❑ Cast walkers

- ▶ Several cast walkers (nonremovable,removable) are available and provide the capability to offload the foot similar to contact casts
- ▶ A significant disadvantage of the cast walker is poor patient compliance if the cast walker is removed

## ❑ Knee walkers

- ▶ Knee walkers are ambulatory assist devices that may be indicated for anyone with a lower extremity issue where weight bearing needs to be avoided
- ▶ More popular in the treatment of diabetic ulcer as a means to offload the foot

# Removable cast walker



## Knee walker



# Therapeutic shoes

- ▶ After healing of the ulcer is achieved
- ▶ prevent recurrent ulceration
- ❑ **Disadvantage**
  - older adult patients or those with proprioception abnormalities, may not be able to maintain their balance
  - Some patients find walking in them difficult, if not impossible

# Wedge shoes

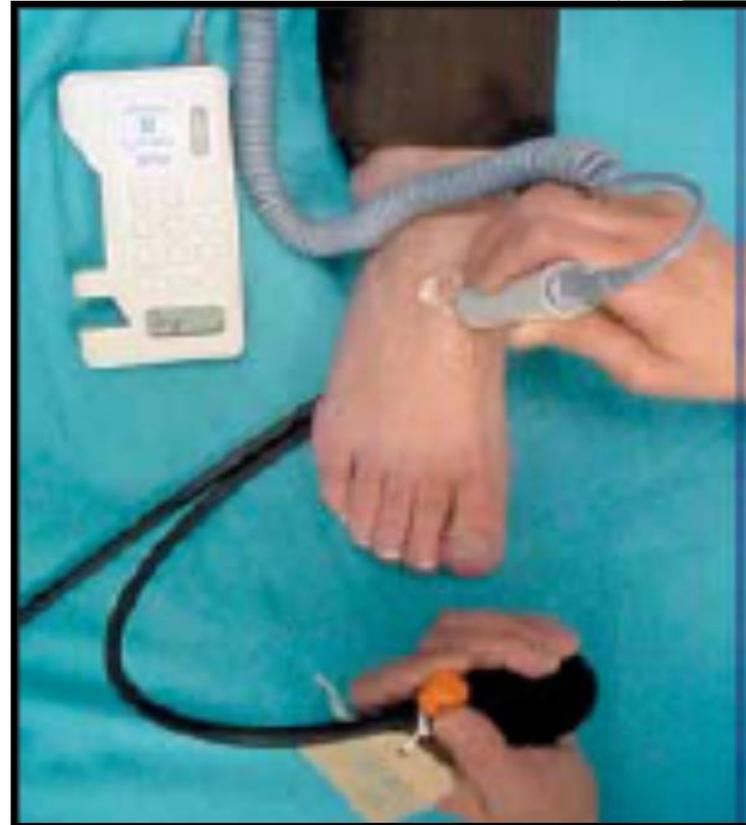


## *Ischemic Ulcer*

- ▶ Assessment of the circulation is an important component of the evaluation of all ulcers particularly those in patients with diabetes
- **Symptoms** and **sign**
  - claudication or extremity pain at rest, diminished or absent pulses, cool temperature, pallor on elevation, or dependent rubor

# *Ischemic Ulcer*

- ❑ Noninvasive vascular studies
  - ankle-brachial index, toe waveforms and pressures, toe-brachial index
  
- Revascularization plays an important in diabetic foot ulcers in patients with peripheral artery disease (to avoid amputation)



(Edmonds & Foster 2006)<sup>4</sup>

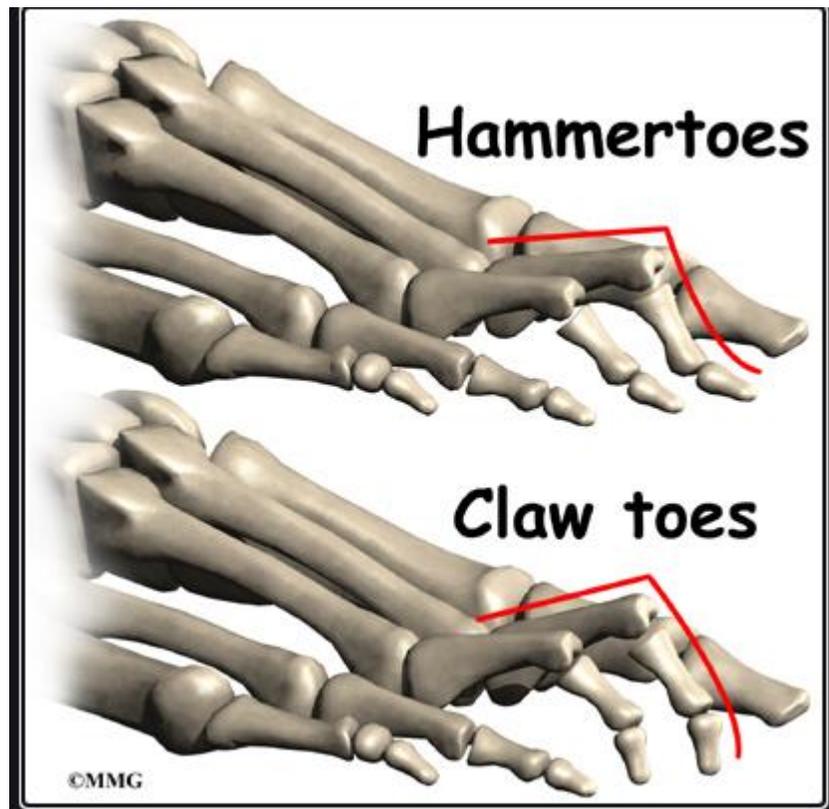
ABPI testing

# *Autonomic Neuropathy*

- Regulates sweating and perfusion to the limb
- Loss of autonomic control inhibits thermoregulatory function and sweating
- Result is **dry, scaly and stiff skin** that is prone to cracking and allows a portal of entry for bacteria

# *Motor Neuropathy*

- Mostly affects forefoot ulceration
- Intrinsic muscle wasting – claw toes
- Equinus contracture



# *Sensory Neuropathy*

- ▶ Loss of protective sensation
- ▶ Starts distally and migrates proximally in “stocking” distribution
- ▶ Large fibre loss – light touch and proprioception
- ▶ Small fibre loss – pain and temperature
- ▶ Usually a combination of the two

# *Charcot arthropathy*

- ▶ Diabetes is the most common cause of neuropathic (Charcot) arthropathy in the western world
- ▶ Incidence as high as **13 percent** in patients with diabetes
- ▶ The pathogenesis is uncertain
- ▶ Combination of mechanical, neuropathic and vascular factors
- ▶ lack of proprioception secondary to peripheral neuropathy  
ligamentous laxity, increased range of joint movement, instability,  
and damage by minor trauma

# *Charcot arthropathy*

- ▶ Recent onset of unilateral warmth, redness, and edema over foot or ankle, often with a history of minor trauma
- ▶ Severity of the pain is typically less than might be expected from the findings
- ▶ Slowly progressing arthropathy with insidious swelling over months or years
- ▶ Deformities are common and can transfer weightbearing to areas that tolerate it poorly and or that may lack sensation
- Ulceration and infection common
- Collapse of the arch of the midfoot can lead to bony prominences on the plantar aspect with later pressure ulceration



# Differential diagnosis

- ▶ Septic arthritis
- ▶ Cellulitis
- ▶ Gout
- ▶ Calcium pyrophosphate arthropathy
- ▶ Osteoarthritis
- ▶ Osteomyelitis

# Treatment

- ▶ Individualized and by a multidisciplinary team including:
  - ✓ Medical experts in joint disease and diabetes
  - ✓ Specialists in foot and ankle surgery and podiatry
- ▶ In the acute active stage **offloading** the foot is the most important intervention with total contact cast. Alternative is crutches or a wheelchair
- ▶ **Offloading** until resolution of edema and erythema , with improvement of radiologic signs and reduction of temperature of the affected foot
- ▶ Bisphosphonate may be an adjunct to therapy in selected patients

# *Goal of treatment*

- ▶ The goal of treatment in patients with chronic disease and joint injury is to maintain a stable and free of ulceration and infection
- ▶ Surgical correction is undertaken in selected patients.
- ▶ Surgical correction of skeletal deformity following nonunion of a fracture in a neuropathic foot has a relatively **high failure** rate, mainly in patients who have active ulceration
- ▶ Surgery should be postponed until the ulcers have healed

# *PROGNOSIS*

- ▶ Disease of the **hindfoot** and **ankle** appears to have a worse prognosis than disease of the midfoot
- ▶ Data are limited regarding whether bisphosphonate treatment improves the long-term outcome
- ▶ Charcot neuroarthropathy can have a significant negative impact on self reported quality of life in patients with diabetes

# *Infected Ulcer*

# Diagnosis of a diabetic foot infection

- ▶ The presence of two or more features of inflammation
  - Erythema
  - Warmth
  - Tenderness
  - Swelling , induration
  - purulent secretions

# Pathogenesis of lower extremity infections

- ▶ Hyperglycemia
- ▶ Sensory and autonomic neuropathy
- ▶ Peripheral arterial disease
- Associated with morbidity and mortality

# Evaluation of a patient with a diabetic foot infection

- ▶ Extent and severity of infection (clinical and radiographic)
- ▶ Underlying factors that predispose to and promote infection
- ▶ Microbial etiology
- ▶ Need for surgical intervention

# Laboratory testing

- ▶ CBC evaluate for leukocytosis
- ▶ Blood glucose
- ▶ Electrolytes
- ▶ Renal function values and acid base status
- ▶ Inflammatory markers such as (**ESR**) and (**CRP**) can be useful for monitoring response to therapy
- ❑ Conventional radiographs to evaluate for bony and soft tissue deformity or abnormalities
- ❑ Formal vascular evaluation in cases where peripheral arterial insufficiency is suspected

# Diagnosis of osteomyelitis

- ❑ The definitive diagnosis of osteomyelitis is made through histologic and microbiologic evaluation of a bone biopsy sample
- ❑ Clinical factors can support diagnosis of osteomyelitis in the absence of biopsy:
  - Grossly visible bone or ability to probe to bone
  - Ulcer size larger than 2 cm<sup>2</sup>
  - Ulcer duration longer than one to two weeks
  - Erythrocyte sedimentation rate (**ESR >70 mm/h**)

# *Radiographic findings of osteomyelitis*

- ▶ Cortical erosion
- ▶ Mixed lucency
- ▶ Soft tissue swelling
- ▶ Sclerosis
- ▶ Bony destruction
- ▶ Periosteal reaction
- ▶ Radiographs may be unremarkable for the first 10 to 14 days following infection
- ▶ approximately 50 to 75 percent of the bone matrix must be destroyed before plain radiographs demonstrate lytic changes

## Osteomyelitis of the toe



Radiograph of the foot demonstrates air in the soft tissues about the 5th toe (black arrowheads). Cortical destruction of the 5th metatarsal head is also seen (white arrow). Irregular contour of the overlying skin represents associated soft tissue ulceration (asterisk).

# Surgical debridement or resection

- ▶ Many patients with osteomyelitis benefit from **surgical resection**
- ▶ Prolonged antibiotic therapy without resection reported success rates comparable to surgery, about 60 to 90%
- ▶ Partial amputations of the foot may adversely alter the biomechanics of the foot, increasing the risk of future ulceration
- ▶ In certain cases, limited surgical debridement combined with prolonged antibiotic therapy may be appropriate

## Extensive surgical debridement or resection

- ▶ Persistent sepsis
- ▶ Inability to receive or tolerate appropriate antibiotic therapy
- ▶ **Progressive** bone deterioration despite appropriate antibiotic therapy
- ▶ Mechanics of the foot are compromised by extensive bony destruction requiring correction
- ▶ Surgery is needed to achieve soft tissue wound or primary closure

# Management of diabetic foot infections

- ❑ Wound management
  - ▶ Debridement of callus and necrotic tissue, wound
  - ▶ Cleansing, and relief of pressure on the ulcer
  - ▶ **Prompt** surgical debridement is critical for cure of abscess, extensive bone or joint involvement, crepitus, necrosis, gangrene
- ❑ Good nutrition
- ❑ Antimicrobial therapy
- ❑ Glycemic control, and fluid and electrolyte balance

# Microbiology of diabetic foot

- ▶ The microbiology of diabetic foot wounds varies with the severity and extent of involvement
- ▶ **Gram-positive cocci** in Superficial infections
- ▶ **Poly microbial** Deep, chronically infected, previously treated ulcers
- ▶ **Anaerobic organisms** in wounds with extensive local inflammation, necrosis or gangrene
- ▶ Organisms cultured from superficial swabs are **not reliable** for predicting the pathogens responsible for deeper infection

# Empiric antibiotic therapy

- ❑ Empiric antibiotic therapy based upon the severity of infection and the likelihood of involvement of resistant organisms:
- ▶ In **mild** infections, an empiric antimicrobial regimen with activity against skin flora including streptococci and *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA] if risk factors are present)

# Empiric antibiotic therapy

- ▶ **Deep ulcers:** an empiric antimicrobial regimen with activity against streptococci, *S. aureus* (and MRSA if risk factors are present), aerobic gram-negative bacilli and anaerobes
- ▶ Oral antibiotics may be appropriate for ulcers that extend to the fascia

## Oral agents for empiric treatment of mild to moderate diabetic foot infections

<b>Regimens with activity against streptococci and staphylococci (MSSA)</b>	<b>Regimens with activity against streptococci and MRSA</b>	<b>Regimens with activity against streptococci, MRSA, aerobic gramnegative bacilli and anaerobes</b>
<b>Cephalexin or</b>	<b>Clindamycin* or</b>	<b>Trimethoprim- sulfamethoxazole PLUS</b>
<b>Dicloxacillin or</b>	<b>Linezolid or</b>	<b>Amoxicillin- clavulanate -OR</b>
<b>Amoxicillin- clavulanate or</b>	<b>Cephalexin or dicloxacillin PLUS</b>	<b>Clindamycin* PLUS</b>
<b>Clindamycin</b>	<b>Trimethoprim- sulfamethoxazole or doxycycline</b>	<b>Ciprofoxacin or levofloxacin or moxifloxacin</b>

## Antibiotic dosing for adults with normal renal function

<b>Cephalexin</b>	<b>500 mg every 6 hours</b>
<b>Dicloxacillin</b>	<b>500 mg every 6 hours</b>
<b>Clindamycin</b>	<b>300 to 450 mg every 6 to 8 hours</b>
<b>Linezolid</b>	<b>600 mg every 12 hours</b>
<b>Trimethoprim- sulfamethoxazole (co-trimoxazole)</b>	<b>2 double-strength tablets (trimethoprim 160 mg and sulfamethoxazole 800 mg per tablet) every 12 hours</b>

## Antibiotic dosing for adults with normal renal function

<b>Doxycycline</b>	<b>100 mg orally every 12 hours</b>
<b>Amoxicillin- clavulanate</b>	<b>875/125 mg every 12 hours</b>
<b>Ciprofloxacin</b>	<b>500 mg every 12 hours (or, if there is concern for Pseudomonas aeruginosa, 750 mg every 12 hours)</b>
<b>Levofloxacin</b>	<b>500 mg every 24 hours (or, if there is concern for P. aeruginosa, 750 mg every 24 hours)</b>
<b>Moxifloxacin</b>	<b>400 mg every 24 hours</b>

# Parenteral regimens

- ▶ Should be used for deeper than fascia infections
- ▶ limb-threatening diabetic foot infections
- ▶ Evidence of systemic toxicity
- ▶ Patients with infection also requiring surgical debridement perioperatively
- we suggest treatment with a broad-spectrum parenteral antibiotic regimen with activity against streptococci, MRSA, aerobic gram-negative bacilli, and anaerobes

## Parenteral agents for empiric treatment of moderate to severe diabetic foot infections

	Dosing (for adults with normal renal function)	Activity against <i>Pseudomonas</i>
<b>Beta-lactam/beta-lactamase inhibitors</b>		
<b>Ampicillin- sulbactam</b>	<b>3 g every 6 hours</b>	<b>No</b>
<b>Piperacillintazobactam</b>	<b>3.375 g every 6 hours or 4.5 g every 6 to 8 hours</b>	<b>Yes, when dosed 4.5 g every 6 hours</b>
<b>Carbapenems</b>		
<b>Imipenem-cilastatin</b>	<b>500 mg every 6 hours</b>	<b>Yes</b>
<b>Meropenem</b>	<b>1 g every 8 hours</b>	<b>Yes</b>
<b>Ertapenem</b>	<b>1 g every 24 hours</b>	<b>No</b>

## Parenteral agents for empiric treatment of moderate to severe diabetic foot infections

	Dosing (for adults with normal renal function)	Activity against <i>Pseudomonas</i>
<b>Combination regimens</b>		
<b>Metronidazole PLUS one of the following:</b>	<b>500 mg every 8 hours</b>	<b>No</b>
<b>Ceftriaxone</b>	<b>1 to 2 g every 24 hours</b>	<b>No</b>
<b>Ceftazidime</b>	<b>1 to 2 g every 8 hours</b>	<b>Yes, when 2 g dose is used</b>
<b>Cefepime</b>	<b>2 g every 8 to 12 hours</b>	<b>Yes, when dosed every 8 hours</b>
<b>Ciprofloxacin</b>	<b>400 mg IV every 8 to 12 hours</b>	<b>Yes, when dosed every 8 hours</b>
<b>Levofloxacin</b>	<b>750 mg IV every 24 hours</b>	<b>Yes</b>
<b>Moxifloxacin</b>	<b>400 mg every 24 hours</b>	<b>No</b>

## Parenteral agents for empiric treatment of moderate to severe diabetic foot infections

	Dosing (for adults with normal renal function)	Activity against <i>Pseudomonas</i>
<b>PLUS one of the following if MRSA coverage is warranted</b>		
<b>Vancomycin</b>	<b>15 to 20 mg/kg every 8 to 12 hours</b>	
<b>Linezolid</b>	<b>600 mg every 12 hours</b>	

## *Targeted therapy*

- ▶ Antimicrobial therapy should be tailored to culture and susceptibility results
- ▶ It is **not necessary** to cover all microorganisms isolated from cultures
- ▶ *S. aureus* and streptococci (group A or B) should **always** be covered, but in polymicrobial infections, less virulent organisms (such as coagulase negative staphylococci and enterococci) may be less important
- ▶ If isolates are resistant to an empiric regimen to which the patient is responding well, broadening the spectrum to include those isolates may not be necessary
- ▶ For those patients who were initiated on parenteral therapy, a switch to an oral regimen is reasonable following clinical improvement

## Duration of therapy

- ▶ Duration of antibiotic therapy should be tailored to individual clinical circumstances
- ▶ Patients with **mild infection** receive oral antibiotic therapy with wound care until infection has resolved (usually about **one** to **two** weeks)
- ▶ Antibiotics need **not be administered** for the entire duration that the wound remains open

# Duration of therapy

- ▶ Patients with infection also requiring **surgical debridement** should receive IV antibiotic in the absence of osteomyelitis, antibiotic therapy should be administered until signs of infection appear to have resolved (**two** to **four** weeks of therapy)
- ▶ Patients requiring amputation of the involved limb should receive IV antibiotic therapy perioperatively
- ▶ If the entire area of infection is **fully resected**, a brief course of **oral antibiotic** therapy (about **a week**) following surgery is usually sufficient

## Time for primary healing

- ▶ Measurements of ulcer size should be taken at every visit
- ▶ The surface area of ulcer should decrease in size approximately **1 to 2** percent a day and a greater than **40 to 50** percent surface area reduction or reduction of ulcer depth by **four weeks**
- ▶ Debridement of necrotic tissue is important for ulcer healing and the chance of diabetic ulcer healing increased **2.5-fold** and doubled when ischemia was assessed at the first visit

## *Time for primary healing*

- ▶ If this rate of progress is not observed evaluation:
  - glycemic control
  - edema, and general health and nutrition
  - **Reevaluated** for soft tissue infection or osteomyelitis, impaired extremity vascular flow or need for more effective offloading or surgical debridement

# Follow-up

- ▶ Close follow-up is important to improvement and to evaluate the need for modification of antimicrobial therapy, further imaging, or additional surgical intervention
- If clinical evidence of **infection persists** beyond the expected duration
- Patient adherence to therapy
- Antibiotic resistance
- Undiagnosed deeper infection (eg, abscess or osteomyelitis)
- **Ischemia** should be evaluated

# Follow-up

- ▶ Wound healing and a decrease in previously elevated **inflammatory markers** signs of clinical resolution particularly in cases of osteomyelitis
- If infection in a clinically stable patient fails to respond to more than one antibiotic course
- Discontinuing antimicrobial therapy a few days (eg, 48 to 72 hours) in order to obtain a biopsy

## *Key Messages*

- ▶ In persons with diabetes, lower extremity complications are a **major cause** of morbidity and mortality
- ▶ The treatment of foot ulcers is glycemic control, infection, off-loading of high-pressure areas, lower-extremity vascular status, and local wound care
- ▶ Antibiotic therapy is not required for uninfected neuropathic foot ulcers

# Follow-up care and ulcer prevention

- ▶ Ulcer recurrence: 40% at one year, 66% at three years, and up to 75% at five years
- ▶ The goals of long term surveillance and care are to maximize ulcer-free, hospital-free, and activity-rich days
- ▶ Ongoing counseling regarding preventive foot care should be given to any patients with existing neuropathy
- ▶ Several measures can markedly diminish ulcer formation, such as avoiding poorly fitting shoes, not walking barefoot, and stopping smoking
- ▶ SGLT2 inhibitors may be associated with an increased risk of amputation should be discontinued