Diabetic Foot Disease

Keystone, July 2013

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President, EASD
European Association for the Study of Diabetes
Who is at risk of Foot Ulceration?

- Neuropathy
- Peripheral Vascular Disease
- Past history of foot ulceration
- Microvascular Complications (especially nephropathy)
- Poor glycemic control
- Cigarette smoking
- Foot deformity
- Amputation
Clinical Consequences of Diabetic Peripheral Neuropathy

PAIN

Burning
Paraesthesia
Hyperaesthesia
Allodynia
Nocturnal-exacerbation

INSENSITIVITY

Foot ulceration;
at least 50%
preventable

NEUROPATHY

Prevalence of Distal Symmetric Polyneuropathy (DSP)

The MONICA/KORA Augsburg Surveys

Michigan Neuropathy Screening Instrument (MNSI) >2

- Control: 8.9%
- IGT: 13.0%
- Diabetes: 27.6%
Painful Neuropathy in the North-West UK

- Community-Based study of >15,000 patients
- Neuropathy assessed using modified NDS and NSS
- 34% had painful symptoms: 21% had significant symptoms ± signs
- Neuropathy 2x more common in Type 2 DM

Abbott et al. *Diabetes Care* 2011; Epub, August 18th.
Diabetic Neuropathy

‘PAIN – God’s greatest gift to mankind’

Paul Brand
Diabetic Peripheral Neuropathy Sensory

Rat Bite

Dr. Abbas
At risk foot
‘The trouble with most doctors is not that they don’t know enough – but that they do not see enough’

Dominic Corrigan
Causal Pathways for Foot Ulceration

- Neuropathy most important component cause (78%)
- Critical triad: neuropathy, deformity, and trauma present in 63%
- Ischemia component cause in 35%
- >80% of ulcers potentially preventable

The Most Common Causal Pathway to Incident Diabetic Foot Ulcers

ACCUMULATION of COMPONENT CAUSES TO FORM A SUFFICIENT CAUSE

COMPLETED CAUSAL CHAIN TO ULCER

NEUROPATHY
BASELINE PATHOLOGY

DEFORMITY
PATHOPHYSIOLOGIC INVOLVEMENT

MINOR TRAUMA
ENVIRONMENTAL EVENT

TIME
ULCERATION
How to assess for Neuropathy?

- Monofilaments
- Vibration
- Pin prick
- Ankle Reflexes
- Composite Score (e.g., modified NDS)
- QST (e.g., Biothesiometer)
- Electrophysiology
‘You do not need expensive equipment to diagnose the ‘at risk’ diabetic foot’

Paul Brand
Bed-Side Instruments
Recommendations
2. Neuropathy Assessment

• 10 g monofilaments tested at 4 sites (MTH 1, 3 & 5 and hallux plantar) AND ONE OTHER OF
  • 128 Hz tuning fork vibration - hallux
  • Pinprick sensation – dorsal hallux
  • Ankle reflexes
  • VPT – biothesiometer/VPT meter
Recently Proposed screening tests

• Ipswich Touch Test
• Vibratip
• Neuropad
The Ipswich Touch Test (IpTT)

- IpTT and 10g MF showed almost perfect agreement.
- Both showed approximately 80% sensitivity and 90% specificity in identifying at-risk feet.
- Excellent PPV (c. 90%) and NPV (c. 80%)
- IpTT a useful screening test for the at-risk foot requiring no equipment

Rayman et al, Diabetes Care 2011:34:1517
N=265
VPT $\geq 25$ V indicative of 'at-risk' feet
$\geq 2/6$ contact sites insensate

<table>
<thead>
<tr>
<th></th>
<th>MF</th>
<th>ITT</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity(%)</td>
<td>81</td>
<td>76</td>
</tr>
<tr>
<td>Specificity(%)</td>
<td>91</td>
<td>90</td>
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</table>
Vibratip

- a pocket-sized, wipe-clean, battery operated disposable device for checking vibration sensation
- Study of 80 patients with varying severity of neuropathy
- Comparison with VPT (biothesiometer), 10 g monofilaments, modified NDS and IpTT.

Bowling et al, 2012
Vibratip

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Bowling et al Diabetic Med 2012.29:1550
Spearman’s Correlation of Vibratip with:

<table>
<thead>
<tr>
<th></th>
<th>Touch Test</th>
<th>VPT</th>
<th>VPT Cutoff</th>
<th>NDS</th>
<th>NDS Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R value</strong></td>
<td>1</td>
<td>0.81</td>
<td>0.96</td>
<td>0.83</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>P Value</strong></td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
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</tbody>
</table>

Sample size = 62.
Neuropad

- A simple visual indicator test to evaluate sympathetic autonomic neuropathy (sweating) in the feet.
- Correlates with NSS, NDS, QST and autonomic function testing as well as IENFD.
- Predicts risk of foot ulceration

Quattrini et al, Diabetologia 2008;51:1046
Tentolouris et al, Diabetes Care 20110;33:1112
Dialysis and Foot Ulceration

- Dialysis is an independent risk factor for foot ulceration.
- When compared to ESRD patients not on dialysis, 4.2x increased risk of foot ulceration.
- Mortality after amputation - 290% increase in hazard for those on dialysis.
- Need for foot care on dialysis units.

Ndip A et al, Diabetes Care 2010;33: 878-880 and 33;1811-1816
Life on Dialysis

Nicholas Evans, BMJ 2012;345:e5262:
“Being on dialysis isn’t really a life: it’s not even half a life.”

Renata Carey, BMJ 2012;345:e4492:
“Dialysis is brilliant, of course, but deeply horrendous.”

Renata Carey, BMJ 2012;345:e4492
“On the dialysis unit, patients suddenly appear with amputations: and very often with heavily bandaged feet, rapidly followed by crutches and then wheelchairs.”
Mortality, Dialysis and Foot Ulceration

• 192 diabetic dialysis patients followed for 2 years

• Overall 2 yr mortality 53%: 59% if foot ulcer at baseline; 74% if amputation: p<0.001.

• Mortality after amputation - 290% increase in hazard for those on dialysis

• Need for foot care on dialysis units

Ndip A et al, 2012
Foot Pressure Studies in Diabetic Neuropathy

- High foot pressures associated with first and recurrent plantar neuropathic ulcers
- Foot Pressure abnormalities precede the appearance of neuropathy
- High foot pressures predict ulcers
- Plantar callus associated with high pressure and predicts ulcer formation

Murray et al, 1996
Semi-Quantitative Foot Pressure Assessment

- Podotrack (PressureStat): a dynamic pressure print map system
- Inexpensive, easy to use in clinic or at home
- Validated by comparison with optical pedobarograph
- All high pressure sites correctly identified by trained observers

‘Coming Events cast their shadows before.’

Thomas Campbell
The PressureStat™ Plantar Pressure Measuring Device
CHARCOT NEUROARTHROPATHY

J-M Charcot 1825-1893

French Physician/Neurologist

transformed Salpetriere, Paris, into major teaching centre

recognized Mitchell’s contribution

Condition named after Charcot at suggestion of Sir James Paget
Charcot neuroarthropathy

Definition

- simultaneous presence:
  - bone and joint destruction
  - fragmentation
  - remodelling

resulting in severe deformity of the foot
PATIENT EDUCATION

Key Question

Does Education alone reduce the incidence of ulceration in high-risk patients?
Can the introduction of a multidisciplinary foot team reduce foot problems?

- 11 yr prospective study of hospital admissions for DF problems in Ipswich
- 62% fall in major amputations
- Total amputations down by 70%
- These improvements followed the introduction of a multidisciplinary foot service

Krishnan et al, Diabetes Care, 2008;31:99
A diabetic foot ulcer should heal if:

- There is adequate arterial inflow
- Any infection is appropriately managed
- Pressure is removed from the wound and its margins
Factors That Enhance Wound Healing

Correct underlying condition

- Control infection
- Vascular reconstruction for patients with severely compromised peripheral circulation
- Adequate glycaemic control for patients with diabetes
- Off-load pressure
- Maintain moist wound healing environment
Factors That Enhance Wound Healing (continued)

Adequate debridement
– Removes infected and non-viable tissue
– May stimulate release of endogenous growth factors
Effect of Debridement on Healing of Diabetic Foot Ulcers


*100 µg rhPDGF-BB per gram sodium carboxymethylcellulose gel.
Total Contact Cast

Advantages

- Forced compliance
- Shortens stride length
- Decrease cadence
- Reduces activity
- Reduces peak pressures
Offloading the DM Wound

Week of therapy

Cumulative Survival

Device

- TCC
- Half Shoe
- Aircast

Armstrong, et al, Diabetes Care, 2001
‘Instant Total-Contact Cast’ vs TCC: controlled trial

• Randomized controlled trial: 38 plantar neuropathic ulcer patients randomized to instant or regular TCC
• No differences in healing times observed
• Instant TCC quicker to apply and cheaper for the duration of treatment
• Any center can apply instant TCC without casting experience
• This treatment could revolutionize the management of plantar neuropathic ulcers

Katz et al, Diabetes Care 2005;28:555
Methods
Standard Total Contact Cast
Methods
DH Walker
Methods
“Instant Total Contact Cast”
When all else fails
Advanced Monitoring using Temperature Assessment ...
Nerve Damage + Mechanical Stress

Inflammation

Ulceration + Faulty Healing

Infection

Vascular Disease

Amputation

Stop
Randomized Study of skin temperature self-monitoring: Control Group

- Standard Therapy (N=58)
  - Therapeutic shoes & insoles
  - Foot specific education
  - Foot care ≤ 10 weeks

Lavery et al, Diabetes Care 2007;30:14
Study Groups:
1.

- Structured Examination Therapy (N=56)
  - Therapeutic shoes & insoles
  - Foot specific education
  - Foot care ≤ 10 weeks
  - Mirror to inspect feet
  - Log book to record findings of examination

Lavery et al, Diabetes Care 2007;30:14
Study Groups: 2

- Temperature Therapy (N=59)
  - Therapeutic shoes & insoles
  - Education
  - Foot care ≤ 10 weeks

- temperature monitoring device
Kaplan-Meier: Survival Analysis Time to Ulceration

Survival Functions

\[ p = .0112 \]

- Enhanced
- Enhanced-censored
- Structured
- Structured-censored
- Standard Therapy
- Standard Therapy - censored
## Home monitoring of skin temperature

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Sample Size</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lavery Diabetes Care 2004</td>
<td>Ulcer history Neuropathy-deformity</td>
<td>N=85 6 mos</td>
</tr>
<tr>
<td>Lavery Diabetes Care 2007</td>
<td>Ulcer history</td>
<td>N=173 15 mos</td>
</tr>
<tr>
<td>Armstrong Am J Med 2007</td>
<td>Ulcer history Neuropathy-deformity</td>
<td>N=225 18 mos</td>
</tr>
</tbody>
</table>
Guidelines Regarding Negative Pressure Wound Therapy (NPWT) in the Diabetic Foot:

Results of the Tucson Expert Consensus Conference (TECC) on VAC Therapy™
NPWT in the Diabetic Foot

A non-pharmacological tool that can influence wound healing
NPWT after partial foot amputations: a randomized trial

• Multi-centre trial in USA
• 162 patients randomized to NPWT or standard treatment: 16 week observation period
• After 16 weeks: NPWT 56% healed, control 39% healed (p=0.04)
• Rate of healing (p=0.005) and rate of granulation (p=0.001) faster in NPWT group
• Trend towards fewer amputations in the NPWT group (p=0.06)

Lavery, APMA, 2005
Armstrong & Lavery, Lancet 2005;366:1704
NPWT in the treatment of diabetic foot ulcers: a randomized trial

- Multi-centre trial in USA
- 342 patients randomized to NPWT or standard treatment: 16 week observation period
- After 16 weeks: NPWT 43% healed, control 30% healed (p=0.007)
- No safety concerns in NPWT or standard moist wound healing control group
- Fewer secondary amputations in the NPWT group (p=0.035)

Blume PA et al, Diabetes Care 2008;31:631
NPWT in the Diabetic Foot

Conclusions

NPWT is a useful non-invasive therapy that, when used appropriately, can accelerate wound healing in the diabetic foot.
The Diabetic Foot

- HBO
HODFU study: Sweden

- Well-designed placebo-controlled, double-blinded RCT
- Chronic neuro-ischaemic or ischaemic foot ulcers
- 94 patients, 5 treatments/week, up to 40 sessions, HBO or HBA
- Complete healing 52 VS 29% overall (p=0.03): in those having >35 dives, 61 VS 27% (p=0.009)
- No major side effects
- HBO may be a useful adjunctive therapy in selected diabetic foot ulcers.

Londahl et al, Diabetes Care 2010;33:998
Ulcer healing

Löndahl et al, Diabetes Care 2010

The HODFU-study
Hyperbaric Oxygen in Diabetic Foot Ulcers

![Graph showing ulcer healing over time with HBOT and Placebo groups, with * p<0.05 and ** p<0.01 annotations.](image-url)
HBO for DFUs: A cohort Study

- Efficacy of HBO for DFU assessed in a wound care network
- 6259 diabetic patients included (760,000 patient days of wound care)
- HBO treated patients less likely to heal and more likely to undergo amputation
- Even after accounting for potential confounders, HBO did not increase likelihood of healing or reduce chance of amputation

Margolis et al, Diabetes Care 2013:epub
Diabetic Foot Wounds in 2013
How much stagnation?

- Dressings
- Topicals
- Infection management
- Amputation Reduction
- Patient Education
- Charcot
Dressings: what do we know?

- ‘For an obstinate ulcer, sweet wine and a lot of patience should be enough’
  - Hippocrates

- Virtually NO EVIDENCE to support the use of any particular dressing
  - Normal dressing qualities: absorption and retention
  - Remember the words of Brand: ‘Dressings deceive both doctor and patient into thinking that by covering the wound they were curing it’
  - Large RCT 3 dressings: none was superior

Knowles EA, The foot in diabetes, 4th edn 2006
RCT of 3 dressings in chronic diabetic foot ulcers

- RCT of 317 patients randomize to one of 3 dressings: N-A, Inadine or Aquacell
- FU for >6 weeks, no osteomyelitis
- Primary endpoint: ulcers healed at 24 weeks
- No differences in healing or recurrence rates observed
- Costs: £15 VS £17 VS £44
- No indication to use more expensive dressings

Jeffcoate et al. Health Technol Assess 2009 Nov;13:1
The Diabetic Foot

• INFECTION
Recognise infection

- Odour
- Pus
- Cellulitis
- Swelling
- Hyperglycaemia
- Pain
- Erythema
- Pyrexia
The common abuses: what antibiotics are not

- Growth promotors
- Wound healing agents
- Household cleaners
- Hand cleaners
- Scalpels
Diabetic Foot Infections

- Tissue from wound base most useful for culture
- Which ulcers should we treat with antibiotics? Very sparse data
- Which antibiotics should be used?
- No indication to treat with antibiotics clinically non-infected neuropathic ulcers
- International guidelines on diagnosing and treating the infected diabetic foot and osteomyelitis now published

Lipsky et al, Clin Infect Dis 2004;38:17
2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections


1Department of Medicine, University of Washington, Veterans Affairs Puget Sound Health Care System, Seattle; 2Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, Oxford; 3Department of Medicine, University of Washington, Veteran Affairs Puget Sound Health Care System, Seattle; 4Divisions of Hospital Medicine and Infectious Diseases, MetroHealth Medical Center, Cleveland, Ohio; 5Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands; 6Southern Arizona Limb Salvage Alliance, Department of Surgery, University of Arizona, Tucson; 7Northern Michigan Infectious Diseases, Petoskey; 8Department of Medicine, University of Manitoba, Winnipeg, Canada; 9Division of Podiatric Surgery, Department of Surgery, Roxborough Memorial Hospital, Philadelphia, Pennsylvania; 10Department of Medicine, Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; 11Department of Orthopaedic Surgery and Rehabilitation, Loyola University Medical Center, Maywood, Illinois; and 12Department of Infectious Diseases, Dron Hospital, Toucoing, France
Diabetic Foot Infections: DFIs: 2012 IDSA Guidelines

- All diabetic foot wounds are colonized
- Classify DFIs into mild, moderate and severe
- Staphylococci remain the commonest infecting organism
- Broad spectrum Abs first in chronic DFIs until the results of deep cultures available
- The creation of foot care teams can improve outcomes

Lipsky et al, Clin Infect Dis 2012;54:e132
Osteomyelitis: Antibiotics alone?

- Retrospective study of 147 cases in a specialist centre
- 147 cases in 5 years
- 18% hospitalized, 23% required surgery
- Osteomyelitis alone may resolve with antibiotics alone especially if localized, e.g., to one digit
- Manchester policy for antibiotic management of diabetic foot OM – frequent use of e.g., Clindamycin: several months of treatment may be required
- Radiologic improvement seen with long-term Abs.

Game and Jeffcoate Diabetologia 2008;51:962
Boulton et al 2012
Attack of the Superbugs

infections. First, they last only days, or at most weeks, limiting sales. And the better the drug, the more likely doctors and hospitals are to keep it on the shelf as a last resort. Most hospitals require that doctors get special approval to prescribe the best new antibiotics. In that regard, what’s good for public health isn’t necessarily good for antibiotic development.

Capricious regulation is another problem, adding to uncertainty and, in turn, the cost of development. For drugs targeted to many common bacterial ailments, the FDA historically required so-called non-inferiority trials. This meant a new antibiotic needed to prove it was generally no worse than existing treatments in order to win regulatory approval. Otherwise, conducting trials to prove a new antibiotic was better than a sugar-pill placebo—or superior to existing drugs—would require huge trials and, in some cases, was simply unethical if it meant asking pa-
Culture of hands for MRSA
Before handwashing

After handwashing
Larvae and MRSA?

• Prospective longitudinal study
  – 13 subjects culture positive MRSA contaminated wounds
• Larvae applied x3-5 applications q4-5 days
  – 12/13 cultures revealed eradication of MRSA

Bowling, et al, Diabetes Care, 2007
Larval Therapy (LT) and Infection?

- Prospective longitudinal study
- 91 patients with infected ulcers treated with LT: impact on bacteriology assessed after 4 days
- LT – significant impact on most bacteria including Staph and MRSA
- No effect on Pseudomonas
- Antimicrobial peptide Lucifensin isolated from maggots

Multidisciplinary team

- Diabetologists
- Interventional Radiologists
- Nurses
- Orthotist
- Patient
- Podiatrist
- Surgeons

No conflicting advice
For one mistake made for not knowing, ten mistakes are made for not looking.

J A Lindsay
“Before I came to this lecture, I was confused. After hearing it I am still confused, but on a higher level”

Enrico Fermi
Barcelona is a Gothic and Modernist marvel situated directly on the Mediterranean Sea. This unique city is renowned all over the world for its quirky, cosmopolitan character which blends style with history.