



## Potential new help for antibiotic stewardship

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Welcome to this issue's Diabetes Digest and commentary. I wish you all a very blessed and happy Christmas, wherever you are.

Diabetic foot infections are one of the most damaging wound complications, frequently leading to hospitalisation, surgery, amputation and, sometimes, death. Increasingly worrying and problematic is the rising occurrence of resistance strains to antibiotics. This paper may give some hope to managing this clinical nightmare.

Pravibismane is a novel product that has antimicrobial and antibiofilm activity against a broad range of Gram-positive and Gram-negative bacteria. It is the first in a new class of microbial bioenergetic inhibitor agents that disrupt energy flow in bacterial membranes, essentially stopping bacterial adenosine triphosphate production, which subsequently halts all bacterial downstream biosynthetic activity.

This was a Phase 1b randomised, double blind, placebo-controlled, multicentre trial in the US. It was designed to examine the safety and efficacy of topical pravibismane gel as an adjunct therapy for infected diabetic foot ulcers (DFU). Five study sites were asked to enrol between 12 and 15 subjects with moderate or severely infected DFU, as per Infectious Disease Society of America infection classification.

Inclusion criteria were:

- Treated with antibiotics for  $\leq 36$  hours prior to presentation, or failure to

antibiotic therapy prior to enrolment.

- Adequate arterial supply determined by palpable pedal pulses; normal Doppler wave forms; toe brachial index  $\geq 0.75$ ; or ankle brachial index  $> 0.9$ .

The researchers recruited 53 subjects, with 39 randomised to the pravibismane treatment group (PTG) and 13 to the placebo control group (PCG).

The study duration was 6–7 weeks with thrice weekly visits over 2–3 weeks for application of pravibismane or the placebo gel. There were three dosage levels for pravibismane, which were determined by DFU size (3, 7.5 and 15  $\mu\text{g}/\text{cm}^2$ ). All subjects received standard care, including sharp ulcer debridement, systemic antibiotic therapy and offloading. Tissue samples were collected at baseline and at the end of the study. All wounds were dressed with provided dressings according to exudate levels.

Subjects were evaluated at the end of treatment, which was 3 days after the last dose, at test of cure (2 weeks after the end of treatment) and the end of the study, 4 weeks after the end of treatment.

Recorded data included: adverse events; ulcer area measurement by 3D digital photography, documentation of any lower-extremity amputations, bacterial reinfection or relapse; and serum levels for systemic exposure to pravibismane. Culture results and clinical examination, were used at the end of the study to assess infection status. Safety parameters included clinical observations of

tolerability and pharmacokinetics.

The microbiologically evaluable population consisted of 44 (83%) subjects. The most commonly isolated baseline pathogens were: methicillin-susceptible *Staphylococcus aureus* in 11 (25.0%); methicillin-resistant *S aureus* in eight (18.2%); *Enterococcus faecalis* in six (13.6%) and *Pseudomonas aeruginosa* in five (11.4%). Pravibismane demonstrated in vitro efficacy against all the aerobic and anaerobic species isolated in this study.

The PTG had a threefold ulcer size decrease compared with PCG (85% versus 30%;  $p=0.27$ ). The incidence of ulcer-related lower-limb amputations was sixfold lower in the pooled PTG 2.6% versus 15.4% in PCG. Pravibismane was well-tolerated and exhibited minimal systemic absorption. In total, 27 (51.9%) subjects experienced an adverse event that required treatment, but none were considered related to the study drug. There were 6 (11.5%) serious adverse events including two subjects in PCG. None of these were considered related to the study drug. Larger studies are needed but these findings suggest that pravibismane is safe and potentially an effective adjunct treatment for infected DFUs.

Lipsky BA, Kim PJ, Murphy B et al (2024) Topical pravibismane as adjunctive therapy for moderate or severe diabetic foot infections: a phase 1b randomized, multicenter, double-blind, placebo-controlled trial. *Int Wound J* 21(4): e14817

Wound Repair Regen

Update of biomarkers to diagnose diabetic foot osteomyelitis: A meta-analysis and systematic review

Readability ✓✓✓  
 Applicability to practice ✓✓✓  
 WOW! Factor ✓✓

1 The authors aimed to evaluate the diagnostic characteristics of biomarkers for diabetic foot osteomyelitis (DFO). They performed a literature search for studies that reported serological markers and DFO before December 2022.

2 In the 19 studies identified, there were 2,854 patients, and 2,134 were included in the meta-analysis. The most common biomarkers were erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and procalcitonin (PCT).

3 None of the biomarkers that were evaluated could be rated as “outstanding” to diagnose osteomyelitis. Based on the areas under the curve, ESR is an “excellent” biomarker, and CRP and PCT are “acceptable” biomarkers to diagnose osteomyelitis.

4 The authors concluded that additional studies are required to determine if the value of biomarkers is improved when they are combined with clinical assessment of probe to bone and radiographs.

Ansert EA, Tarricone AN, Coye TL, et al (2024) Update of biomarkers to diagnose diabetic foot osteomyelitis: A meta-analysis and systematic review. *Wound Repair Regen* 32(4): 366–76

J Wound Care

Dehydrated Amnion Chorion Membrane versus standard of care for diabetic foot ulcers: a randomised controlled trial

Readability ✓✓✓✓  
 Applicability to practice ✓✓✓✓  
 WOW! Factor ✓✓

1 This prospective, multicentre, randomised controlled trial (RCT) evaluated the effectiveness of a dehydrated Amnion Chorion Membrane (dACM; Organogenesis) versus standard of care (SoC) alone in complex diabetic foot ulcers (DFUs).

2 Subjects (n=218) with a DFU extending into dermis, subcutaneous tissue, tendon, capsule, bone or joint were allocated equally to two treatment groups: dACM (plus SoC); or SoC alone. The primary endpoint was frequency of wound closure determined by a Cox analysis that adjusted for duration and wound area. Kaplan-Meier analysis was used to determine median time to complete wound closure (CWC).

3 Wound closure for the dACM plus SoC group was statistically superior to the SoC alone group.

4 The authors concluded that dACM increased the frequency, decreased the median time, and improved the probability of CWC when compared with SoC alone

Cazzell SM, Caporusso J, Vayser D et al (2024) Dehydrated Amnion Chorion Membrane versus standard of care for diabetic foot ulcers: a randomised controlled trial. *J Wound Care* 33(Suppl 7): S4–14

Am J Phys Med Rehabil

Sensorimotor training improves gait, ankle joint proprioception, and quality of life in patients with diabetic peripheral neuropathy

Readability ✓✓✓  
 Applicability to practice ✓✓✓  
 WOW! Factor ✓✓

1 The researchers investigated the effect of sensorimotor training on gait, ankle joint proprioception, and quality of life in patients with diabetic peripheral neuropathy (DPN).

2 This was a prospective, single-blind, randomised controlled trial of 40 patients with DPN, split randomly into sensorimotor training (n=20) and control (n=20) groups. Both groups attended 30-minute awareness sessions about diabetes and foot care every fortnight. The sensorimotor group received 6 weeks of sensorimotor training. Spatiotemporal gait parameters, proprioception accuracy of the ankle joint and quality of life were measured before and after the 6-week intervention.

3 The sensorimotor training group had significant improvements in all outcomes (p<0.001), while the control group showed significant changes in quality of life only (p=0.03).

4 Sensorimotor training may improve spatiotemporal gait parameters, ankle joint proprioception and quality of life of patients with DPN.

Saleh MSM, Elbanna RHM, Abdelhakiem NM et al (2024) Sensorimotor training improves gait, ankle joint proprioception, and quality of life in patients with diabetic peripheral neuropathy: a single-blinded randomized controlled trial. *Am J Phys Med Rehabil* 103(7): 638–44

“These findings suggest that pravibismane is safe and potentially an effective adjunct treatment for infected DFUs”

## Medicine

### Efficacy and safety of hyperbaric oxygen therapy for diabetes peripheral neuropathy: A systematic review and meta-analysis

Readability ✓✓✓✓  
Applicability to practice ✓✓  
WOW! Factor ✓✓✓

**1** The authors aimed to evaluate the clinical efficacy and safety of hyperbaric oxygen therapy (HBOT) for diabetic peripheral neuropathy (DPN) using a systematic review and meta-analysis.

**2** A comprehensive search was conducted across several databases for relevant randomised controlled trials published before July 2022.

**3** Fourteen trials were included in the final analysis, comprising 675 patients in the HBOT group and 648 in the standard therapy (ST) group. The HBOT group demonstrated a significantly higher effective treatment rate compared to the ST group ( $p < 0.001$ ). Additionally, the HBOT group showed significant improvements in nerve conduction velocity. Six adverse events were reported in the HBOT group, while no adverse events occurred in the ST group, with no significant difference between the 2 groups.

**4** The authors concluded that HBOT significantly enhances treatment efficacy and nerve conduction velocity in patients with DPN, with few adverse events, making it a safe and effective adjunctive therapy for DPN.

Weng J, Ren H, Guo Q et al (2024) Efficacy and safety of hyperbaric oxygen therapy for diabetes peripheral neuropathy: A systematic review and meta-analysis. *Medicine (Baltimore)* 103(36): e39699

## Int Wound J

### Recurrence rates after healing in patients with neuroischemic diabetic foot ulcers healed with and without sucrose octasulfate-impregnated dressings

Readability ✓✓✓✓  
Applicability to practice ✓✓✓✓  
WOW! Factor ✓✓✓

**1** The aim of this study was to compare recurrence rates in a 1-year follow-up of healed neuroischaemic diabetic foot ulcers (DFUs) after treatment with or without sucrose octasulfate impregnated dressings.

**2** A 1-year prospective study with two arms was conducted on 92 patients with healed neuroischaemic DFUs. They were divided into two groups – treatment group (patients healed with a sucrose octasulfate-impregnated dressing) and control group (patients treated with other local therapies). The main outcome as ulcer recurrence after wound healing within 1 year follow-up.

**3** Fourteen (28%) patients in the treatment group had a reulceration event compared to 28 (66.7%) in the control group.

**4** The authors concluded that sucrose octasulfate-impregnated dressings can decrease recurrence rates of neuroischaemic DFUs more effectively than neutral dressings.

Lázaro-Martínez JL, García-Madrid M, Bohbot S et al (2024) Recurrence rates after healing in patients with neuroischemic diabetic foot ulcers healed with and without sucrose octasulfate-impregnated dressings: A 1-year comparative prospective study. *Int Wound J* 21(10): e70028

## Diabetologia

### Can the introduction of a 12-lead ECG help reduce mortality in those presenting with foot ulceration to multidisciplinary diabetic foot clinics?

Readability ✓✓✓  
Applicability to practice ✓✓✓✓  
WOW! Factor ✓✓✓

**1** The risk of dying within 2 years of presentation with diabetic foot ulceration (DFU) is over six times the risk of amputation, with CVD the major contributor. Using an observational evaluation of a real-world implementation pilot, we aimed to assess whether for those presenting with DFU, introducing a 12-lead ECG into routine care followed by appropriate action was associated with reduced mortality.

**2** Ten multidisciplinary diabetic foot services in England participated in a pilot project introducing 12-lead ECGs for new attendees with foot ulceration.

**3** Of the 3,110 people recorded at a participating unit during the pilot, 33% (1,015) were recorded as having received an ECG. Overall mortality at the participating units was not significantly reduced at 2 or 5 years,

**4** The signals of potential mortality benefit among those who had an ECG suggest that clinical teams may wish to consider this, if they are in a position to do so.

Valabhji J, Holman N, Collins N et al (2024) Can the introduction of a 12-lead ECG help reduce mortality in those presenting with foot ulceration to multidisciplinary diabetic foot clinics? An observational evaluation of a real-world implementation pilot in England. *Diabetologia* 67(7): 1304–14