# POEMs

## *Patient-Oriented Evidence That Matters*

### Cycled Hyperbaric Oxygen Improves the Healing of Diabetic Foot Ulcers

#### Clinical Question

Is topical oxygen effective in hastening the healing of refractory diabetic foot ulcers?

#### Bottom Line

Hyperbaric oxygen provided with a device that cycles oxygen from high pressure to low pressure increased the likelihood of complete healing of diabetic foot ulcers when combined with standard dressing and an offloading boot. The study was small, and fewer than one-half (41.7%) of the patients responded after three months of treatment. (Level of Evidence = 1b–)

#### Synopsis

The investigators enrolled 73 patients with diabetes mellitus who had been recruited from wound centers. The patients had full-thickness diabetic foot ulcers between 1 $cm^2$ and 19 $cm^2$ and had been treated for at least four weeks. They were observed for an additional two weeks, treated with dressing and a rocker sole boot, and were enrolled in the study if they did not have at least a 30% decrease in wound area with this treatment. Using concealed allocation, the study patients were treated with a closed chamber device that provided hyperbaric oxygen cycled between 10 mb and 50 mb (Hyperbox) or a sham device that circulated nonpressurized ambient air. Patients used the device 90 minutes each day five times a week. Using intention-to-treat analysis, after 12 weeks of treatment, 41.7% of patients who received oxygen had complete wound healing compared with 13.5% who received sham treatment ($P$ = .01). For patients without total healing, oxygen therapy was discontinued, and usual care was continued for up to one year. By 12 months (nine months after discontinuing hyperbaric oxygen), 56% of patients who received oxygen had complete healing compared with 27% of patients who received sham treatment. Adverse events were reported in both groups; none were related to the device.

**Study design:** Randomized controlled trial (double-blinded)

**Funding source:** Industry

**Allocation:** Concealed

**Setting:** Outpatient (specialty)

**Reference:** *Frykberg RG, Franks PJ, Edmonds M, et al.; TWO2 Study Group. A multinational, multicenter, randomized, double-blinded, placebo-controlled trial to evaluate the efficacy of cyclical topical wound oxygen (TWO2) therapy in the treatment of chronic diabetic foot ulcers: the TWO2 study.* Diabetes Care. *2020;43(3):616-624.*

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### Increased Daily Steps Associated with Reduced All-Cause Mortality

#### Clinical Question

Is daily step count and the intensity of steps associated with the risk of premature mortality?

#### Bottom Line

This study found that a greater number of daily steps was significantly associated with lower all-cause mortality. Step intensity was not significantly associated with mortality after controlling for total daily steps. (Level of Evidence = 1b)

#### Synopsis

The investigators reviewed data obtained from the National Health and Nutrition Examination Survey focusing on participants who were asked to wear a hip accelerometer during waking hours

for a seven-day period from 2003 to 2006. Individuals with at least one day of valid wear (at least 10 hours) were included. Additional data collection included demographic information (e.g., age, sex, education), smoking status, alcohol intake, and diagnoses of chronic medical conditions (e.g., diabetes mellitus, heart disease, stroke, cancer, chronic bronchitis). In addition to counting steps, step intensity was estimated based on extended bouts of stepping and peak one-minute and 30-minute cadences. Assessments of mortality occurred via the U.S. National Death Index.

Participants (N = 4,840) took a mean of 9,124 steps per day. The incidence of all-cause mortality was 76.7 per 1,000 person-years for individuals who took fewer than 4,000 steps per day; 21.4 per 1,000 person-years for individuals who took 4,000 to 7,999 steps per day; 6.9 per 1,000 person-years for individuals who took 8,000 to 11,999 steps per day; and 4.8 per 1,000 person-years for individuals who took at least 12,000 steps per day. After controlling for total steps per day, greater step intensity was not significantly associated with lower mortality.

**Study design:** Cohort (prospective)

**Funding source:** Foundation

**Setting:** Population-based

**Reference:** *Saint-Maurice PF, Troiano RP, Bassett DR Jr., et al. Association of daily step count and step intensity with mortality among US adults.* JAMA. *2020;323(12):1151-1160.*

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## Terbinafine and Itraconazole Are Most Effective for Toenail Onychomycosis

### Clinical Question

What is the preferred monotherapy for the treatment of toenail onychomycosis?

### Bottom Line

For toenail onychomycosis, continuous terbinafine (Lamisil), 250 mg, and continuous itraconazole (Sporanox), 200 mg, for 12 to 24 weeks are the preferred therapies. (Level of Evidence = 1a–)

### Synopsis

Network meta-analyses can include direct comparisons (drug A vs. drug B in individual trials) and indirect comparisons (comparing drug A with drug C by linking studies of A vs. B and B vs. C). The researchers performed an appropriate search, and, of the 10,845 studies initially identified, 75 met the inclusion criteria, but only 26 reports of 31 clinical trials provided outcome data regarding cure rates or adverse events that could be used in the analysis. The included studies had a total of 8,136 patients and reported eight treatment regimens, including some with the same drug given continuously or in a pulsed fashion (i.e., daily for one week of a month). Most studies treated patients for 12 to 24 weeks, and the study drugs included ciclopirox 8% solution (Loprox), efinaconazole 10% solution (Jublia), fluconazole (Diflucan), itraconazole, terbinafine, and tavaborole 5% solution (Kerydin). The researchers used conventional methods for data abstraction, quality assessment, and analysis.

Of the 31 trials, only five were judged to be at overall low risk of bias. Most studies failed to describe randomization procedures or allocation concealment, 52% failed to mask participants, and 64% failed to mask outcome assessors. Itraconazole, 200 mg, and terbinafine, 250 mg, were most effective, based on placebo-controlled trials. Continuous regimens were more effective than pulsed regimens. This is consistent with the results based on direct and indirect comparisons. Continuous terbinafine and continuous itraconazole were most likely to be effective for mycologic cure. Adverse events did not differ much among the drugs; itraconazole was the safest.

**Study design:** Meta-analysis (randomized controlled trials)

**Funding source:** Self-funded or unfunded

**Setting:** Various (meta-analysis)

**Reference:** *Gupta AK, Foley KA, Mays RR, et al. Monotherapy for toenail onychomycosis: a systematic review and network meta-analysis.* Br J Dermatol. *2020;182(2):287-299.*

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## C-Reactive Protein Is the Most Useful Biomarker for Diagnosis of Outpatient CAP

### Clinical Question

How accurate are biomarkers C-reactive protein (CRP), procalcitonin, and leukocytosis in the diagnosis of community-acquired pneumonia (CAP) in adults with respiratory symptoms?

## Bottom Line

This review found that the best evidence supports CRP as the most useful and accurate biomarker for diagnosing CAP in adults presenting with lower respiratory tract symptoms. Procalcitonin has a good positive likelihood ratio (LR+) but a minimally useful negative likelihood ratio (LR–). Leukocytosis has only modest accuracy that is minimally clinically useful. (Level of Evidence = 1b)

## Synopsis

The investigators searched PubMed and reference lists of pertinent articles for studies that evaluated the accuracy of readily available biomarkers in adult patients who presented with symptoms of acute respiratory infection and those with clinically suspected pneumonia. The authors included studies with at least one biomarker test and an acceptable reference standard (chest radiography or computed tomography) performed on all participants. They did not exclude any studies based on country, year, or language. Two or more individuals independently reviewed potential studies for inclusion and risk of bias using a standard evaluation tool. Discrepancies were resolved through consensus discussion. The authors ended with 14 studies with a total of 6,599 patients. One-half of the studies occurred in the emergency department, and one-half occurred in the primary care setting. Of the 14 studies, eight were scored at low risk of bias, with the remaining six studies considered at moderate risk of bias.

CRP was the most accurate test (less than 1 mg per dL [10 mg per L]; LR– = 0.27, and greater than 2 mg per dL [20 mg per L], 5 mg per dL [50 mg per L], and 10 mg per dL [100 mg per L]; LR+ = 2.08, 3.68, and 5.79, respectively). Procalcitonin had a good LR+ (greater than 0.25 mcg per L and 0.50 mcg per L; LR+ = 5.43 and 8.25, respectively) but a minimally useful LR–. Leukocytosis was only modestly accurate (greater than 9.5 to 10.5; LR+ = 3.15). Based on existing clinical decision rules using signs and symptoms, if the probability of CAP is 25% or less, a CRP of less than 20 mg per L decreases the probability of CAP to less than 10%, making imaging unlikely to be clinically useful and unnecessary.

**Study design:** Meta-analysis (other)

**Funding source:** Self-funded or unfunded

**Setting:** Various (meta-analysis)

**Reference:** *Ebell MH, Bentivegna M, Cai X, et al. Accuracy of biomarkers for the diagnosis of adult community-acquired pneumonia: a meta-analysis.* Acad Emerg Med. *2020;27(3):195-206.*

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**Editor's Note:** Dr. Ebell is deputy editor for evidence-based medicine for *AFP* and cofounder and editor-in-chief of Essential Evidence Plus, published by Wiley-Blackwell. Dr. Shaughnessy is an assistant medical editor for *AFP*. ■