Symptoms Key to Detecting Diabetic Infections

Surprisingly, culturing for microorganisms is not the best way to diagnose infection in foot lesions.

BY MARK S. LESNEY
Senior Editor

CHICAGO — Clinical symptoms are critical in distinguishing between uninfected and mildly infected diabetic foot lesions, Warren S. Joseph, D.P.M., reported at the Vascular Annual Meeting.

For instance, lack of cellulitis indicates lack of infection, as does good granulation. If the wound is purulent, it is infected.

Surprisingly, culturing the wound for microorganisms is not the best way to diagnose infection. This is because even noninfected diabetic foot lesions are "wound toilets" or, less bluntly, they have a significant "bioburden or bioload" of microorganisms that are simply colonizing the lesion, said Dr. Joseph of the Veterans Affairs Medical Center in Coatesville, Pa.

Just because an ulcer is colonized does not mean it is infected, he explained. However, in patients whose diabetic foot lesions are colonized but not infected, physicians may feel uncomfortable about doing nothing, Dr. Joseph said. They know the microbes are there, and they feel compelled to provide treatment, he said.

In this situation, topical treatments such as those with broad-spectrum activated silver are better than systemic antibiotics. And yet there is little evidence that topical antibiotics have any benefit for healing wounds, he said. In addition, they have little effect on preventing infection.

"Antibiotics do not heal wounds, antibiotics treat infection," Dr. Joseph said, adding that he could not overemphasize the point that systemic antibiotics do not have a place in treating noninfected wounds.

Why? Because the first strain of vancomycin-resistant *Staphylococcus aureus* was found in a diabetic foot wound; it showed up in a swab culture of a clinically noninfected wound.

According to Dr. Joseph, the Infectious Diseases Society of America classification system developed last year defines mild infection as that extending less than 2 cm (www.idsociety.org). Moderate infection is greater than 2 cm and/or shows spread, streaking, or gangrene, but is still localized to the foot. Severe infections are systemic and life-threatening.

It is a misconception, Dr. Joseph pointed out, that all diabetic foot infections are polymicrobial. Virtually all diabetic foot infections have been shown to be caused by just two microorganism types—*Staphylococcus aureus* and group B streptococci. "This is great news, because when you think about what antibiotics you need for staph and strep—just about anything," he said. "Those broad-spectrum drugs we have been using all these years we probably do not need, with one small caveat—there has been an incredible increase in prevalence of methicillin-resistant staph in [the] diabetic foot." The bottom line is that 40% or more of all diabetic foot staph infections are methicillin resistant.

The number of diabetic foot patients who presented with methicillin-resistant *Staphylococcus aureus* doubled between 1999 and 2002, he said.

Given the variety of alternatives available—anything you would use for staph or strep throat—Dr. Joseph said: "Do not use ciprofloxacin in the infected diabetic foot."

The reasoning is that it has poor activity against staph and strep, and it is a single-step mutation to getting staph or strep resistant to ciprofloxacin.

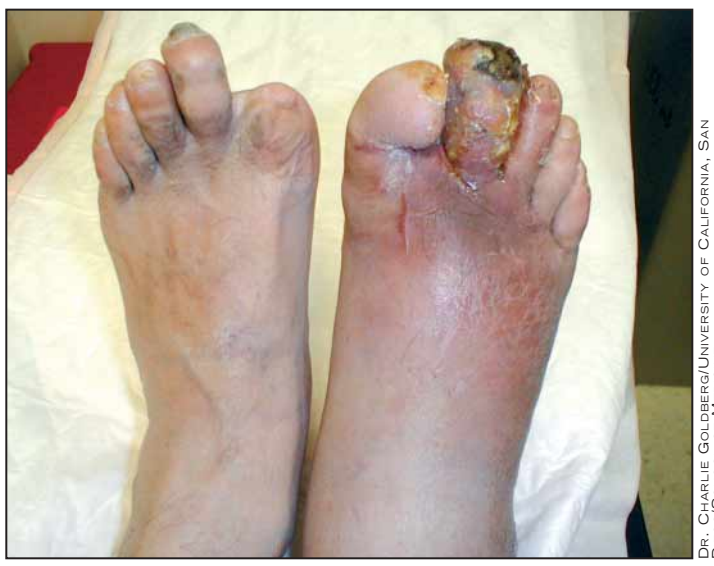
"You might have a nice big S sitting next to the cipro line, but give that patient the drug, [and] within a week it's going to turn to an R."

Dr. Joseph said that he believes ultimately it will be shown that severe infections will respond to antibiotics directed against staph and strep, even if there are corresponding anaerobic microbes present.

He used the analogy of a snake: Remove the head (staph and strep), and the rest dies.

However, he stated that the clinical data are not there just yet to support advising against the use of broad-spectrum antibiotics for such infections, and so he could not recommend it.

Dr. Joseph disclosed financial relationships with Merck and Pfizer. ■



DR. CHARLIE GOLDBERG/UNIVERSITY OF CALIFORNIA, SAN DIEGO/SCHOOL OF MEDICINE

Poorly controlled diabetes led to peripheral arterial disease, neuropathy, and severe infection in a patient's right foot. Note that the patient has lost the left great toe to a prior infection.

Reverset Effective When HIV Regimens Fail

BY CHARLENE LAINO
Contributing Writer

RIO DE JANEIRO – The novel nucleoside reverse transcriptase inhibitor Reverset is poised to become the newest member of the oldest class of antiretroviral agents, with researchers reporting its promise for HIV-infected patients for whom current antiretroviral regimens have failed and who have NRTI resistance.

In a 16-week randomized trial of nearly 200 treatment-experienced patients, 54% of those treated with 200 mg of Reverset daily experienced more than a 1.0-log drop in viral load (the trial's definition of response to therapy), compared with 40% of patients who received a placebo, Calvin Cohen, M.D., said at the International AIDS Society Conference on HIV Pathogenesis and Treatment.

Reverset was effective in patients with HIV resistant to other commonly used nucleoside analog reverse transcriptase inhibitors, including the two-thirds of patients with the M41L multiple thymidine analog mutation, Dr. Cohen, research director for both Harvard Vanguard Medical Associates and Community Research Initiative of New England in Boston, reported at a late-breaking session.

Formerly known as D-d4FC and yet to be assigned a generic name, Reverset is well tolerated and can be given once daily, he said. Reverset is under development by Incyte Inc., which helped fund the research. "Reverset appears to be an active, potent drug in treatment-experienced patients," Dr. Cohen told this newspaper. "Very few of our nucleosides have maintained the kind of activity we're seeing in patients with resistant virus."

Mark A. Wainberg, Ph.D., director of the McGill University AIDS Centre, Montreal, and moderator of the late-breaking session, agreed.

"Reverset appears to be an excellent addition to our armamentarium of nucleoside reverse transcriptase inhibitors. It is well tolerated and active against virus with various mutations," he said.

'An excellent addition … It is well tolerated and active against virus with various mutations.'

DR. WAINBERG

Dr. Cohen said the new trial follows earlier studies suggesting that Reverset does not appear to cause mitochondrial toxicity or elevated lactate levels—side effects associated with other NRTIs.

For the Phase IIb trial, the researchers randomized 199 treatment-experienced patients who were failing their current regimen to one of three doses of Reverset (50 mg, 100 mg, or 200 mg) or placebo. The patients had a mean baseline viral load of 31,600 copies/mL and most had NRTI-associated mutations: 60% had the M184V mutation, 66% had M41L, 50% had four to six thymidine analogue mutations, and 6% had K65R. After 2 weeks, patients who received the 200-mg dose of Reverset as add-on therapy achieved a drop in viral load of 0.7 $\log_{10}$ copies/mL, compared with a drop of 0.03 $\log_{10}$ copies/mL in the placebo arm. By 16 weeks, patients who received 200 mg of Reverset as add-on therapy had a drop in viral load of 1.2 $\log_{10}$ copies/mL, compared with a drop of 0.8 $\log_{10}$ copies/mL in placebo patients.

The results were best in patients who did not receive lamivudine or emtricitabine, which have a similar chemical structure to Reverset, Dr. Cohen said. In this subset, 80% of patients who had Reverset achieved a barely discernible viral load of less than 50 copies/mL, compared with 25% on placebo. Using a combination of drugs that that target different sites within the virus packs a more powerful punch, he explained.

Both the 100-mg and 50-mg doses of Reverset were less effective than the 200-mg dose, so the higher dose will be used for future study, Dr. Cohen said.

Side effects were generally mild; however, 50% of patients receiving 200 mg of Reverset with didanosine showed an elevation of pancreatic enzymes and two patients on 100 mg of Reverset developed symptomatic pancreatitis. ■

Epstein-Barr Virus In Pregnancy Poses Little Peril to Fetus

ST. PETE BEACH, FLA. — Maternal infection with the Epstein-Barr virus does not appear to represent a major teratogenic risk, Meytal Avgil, M.D., reported at the annual meeting of the Teratology Society.

The herpesvirus—and the cause of infectious mononucleosis—has not been well studied in pregnancy, but in a recent prospective study, the rate of major anomalies was 5% in a group of more than 200 EBV-exposed pregnancies, and 3% in a group of nearly 1,200 controls.

The difference between groups was not statistically significant, and the rates were within the expected baseline risk for the general population, said Dr. Avgil of Hebrew University, Jerusalem.

Furthermore, the anomalies did not follow any specific pattern in the EBV group, and were similar in the two groups, she noted.

There also were no differences in the rate of live births, miscarriages, or elective terminations of pregnancy between the two groups; the median birth weight of infants was similar in both groups, ranging from about 3,200 to 3,300 g.

The median gestational age at delivery was 40 weeks in both groups.

—Sharon Worcester