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High-dose Oral Vitamin D_3 Significantly Reduced Effects of Sunburn

Amy Karon

When taken within an hour, a single dose of at least 100,000 IU vitamin D_3 rapidly attenuates sunburn, according to results of a randomized, double-blind, placebo-controlled pilot study of 25 healthy adults.

This is the first in vivo study to evaluate whether vitamin D_3 can modulate acute inflammation in target tissues, Jeffrey F. Scott, MD, wrote in a poster presented at the annual meeting of the Society for Investigative Dermatology. The findings "have broad implications for the role of vitamin D in skin homeostasis and suggest that oral vitamin D may be clinically therapeutic for its immunomodulatory properties," he and his coauthors concluded.

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Study participants were exposed to ultraviolet radiation to induce experimental sunburn on the left arm. One hour later, they received either oral placebo or vitamin D_3 in a dose of 50,000 IU, 100,000 IU, or 200,000 IU. After 24 hours, recipients of the 100,000 IU and 200,000 IU doses had a marked, sustained reduction in skin redness compared to recipients of placebo or the 50,000 IU dose.

Higher doses of vitamin D_3 also produced significant decreases in skin levels of tumor necrosis factor–α (TNF-α) and inducible nitric oxide synthase (iNOS), compared with placebo.

Notably, 48 hours after sunburn, hematoxylin and eosin histology of punch biopsies showed that participants who received 200,000 IU of vitamin D_3 had the least structural damage to the skin, while placebo recipients had the most damage. Expression profiling also linked vitamin D_3 treatment with upregulation of genes associated with skin barrier repair.

Studies continue to document diverse biologic effects of vitamin D, including "modulation of immune response, inflammatory disease, cardiovascular health, and carcinogenesis," reported Dr. Scott, a resident in dermatology at University Hospitals Cleveland Medical Center. Vitamin D_3 has also been shown to suppress inflammatory mediators and induce autophagy. Previous research by Dr. Scott's group demonstrated that oral D_3 induced similar protective effects in a mouse model of chemical skin injury. Treatment inhibited proinflammatory cytokines and chemokines within the skin, including iNOS and TNF-α.

The current study also included a control phase in which participants underwent experimental sunburn on the right arm without any treatment. Forty-eight hours later, punch biopsies revealed high levels of iNOS and TNF-α, with increased expression of proinflammatory genes.

During the subsequent experimental phase, seven participants were assigned to receive placebo and six to receive vitamin D_3. After treatment, participants with the highest serum D_3 levels had significantly decreased skin redness, compared with participants with lower serum D_3 levels. Higher serum vitamin D_3 levels were also associated with significant upregulation of skin barrier repair genes and of arginase-1, a cytosolic enzyme that helps mediate anti-inflammatory activity.

"Arginase-1 may be a clinically useful tissue biomarker for monitoring the immu-

nomodulatory effects of vitamin D_3 in humans," the researchers concluded.

Disclosures: The National Institute of Arthritis Musculoskeletal and Skin Diseases and the National Institutes of Health supported the work. Dr. Scott had no relevant financial disclosures.

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Expires May 23, 2018

Women Less Likely to Be Diagnosed With Sleep Disorders

Eli Zimmerman

Women are less likely to be diagnosed with and treated for sleep-disordered breathing (SDB), despite having symptoms similar to men's. Underdiagnosis of SDB in women may have dire consequences, as symptoms—specifically, snoring and excessive daytime sleepiness (EDS)—correlate with increased risk for hypertension and diabetes, regardless of gender, according to Eva Lindberg, PhD, Professor in the Department of Medical Sciences, Respiratory, Allergy, and Sleep Research at Uppsala University, Sweden, and her colleagues.

In a survey of 10,854 subjects, 14% of women reported being diagnosed with obstructive sleep apnea (OSA), compared with 25% of men. Furthermore, 9% of women reported receiving any OSA treatment, compared with 16% of men (*Sleep Med*. 2017. doi: 10.1016/j.sleep.2017.02.032).

The mean age of patients at baseline was 41. Mean BMI was 25.4 for men and 24 for women.

On initial testing, about three times as many men as women reported having issues with snoring and no EDS (19% vs. 6% respectively), while more women reported the opposite, EDS but no snoring (19% vs. 11%, respectively). A slightly larger percentage of men reported having both symptoms (7.3% vs. 4.5%).

Investigators hypothesized that the disparity between women and men reporting problems with snoring may be caused by gender expectations. "It is more probable that SDB is still assumed to be a condition associated predominantly with men, and women feel ashamed of reporting these symptoms and seeking medical advice," they noted. These gender expectations may "contribute to females being less inclined to seek medical advice due to SDB symptoms."

In a follow-up survey conducted 11 years later, 1,716 patients reported a new diagnosis of hypertension and 319, of diabetes. While incidence for both was greater in men than in women (hypertension, 18.6% vs. 15.8%; diabetes, 3.6% vs. 2.4%), investigators found "after adjusting for BMI and snoring at baseline, none of these gender differences remained significant."

Similar disparities were found in populations with newly developed sleep apnea, and in treatment of those who had reported having both symptoms on the initial survey.

Providers' perceptions of SDB as a predominantly male condition may lead them

Credit: Monkey Business Images / Shutterstock

to overlook symptoms in female patients that would otherwise be cause for further testing, the researchers noted.

"[Even] among health professionals, SDB is still usually attributed to a male population and female patients are therefore less frequently asked about the cardinal symptoms of snoring and sleepiness and do not therefore undergo sleep recordings," the researchers say. "Also, among patients with obesity hypoventilation syndrome, females are generally diagnosed when the disease is more advanced and significantly more frequently develop acute disease before achieving treatment."

Dr. Lindberg and her team suggest engaging female patients in discussions about SDB symptoms more frequently, as well as referring symptomatic patients to participate in a sleep study.

This study was limited by the nature of the data (self-report rather than assessment with the Epworth Sleepiness Scale).

Disclosures: The study was funded by grants from the Norwegian Research Council, the Icelandic Research Council, Aarhus University, the Swedish Heart-Lung Foundation, and the Estonian Science Foundation. The investigators report no relevant financial disclosures.

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Expires May 30, 2018

RA Treatment Delays Raise Risk for Long-term Disability

Bianca Nogrady

Initiating disease-modifying antirheumatic drugs within six months of rheumatoid arthritis (RA) diagnosis is associated with significantly lower disability scores over the long term, new research suggests.

Better diagnosis and access to early treatment has also likely played a role in a global decline in mortality from RA over a 25-year period, according to an analysis of data from the World Health Organization (WHO) and the United Nations (UN). But the decline has occurred unequally across countries.

Impact of early treatment on disability

In the first of two separate studies published in *Arthritis & Rheumatology*, UK researchers followed 602 patients from the Norfolk Arthritis Register for 20 years, starting in 1990-1994, and collected clinical data at baseline and years 1-3, 5, 7, 10, 15, and 20.

Their analysis suggested that patients who did not receive treatment with disease-modifying antirheumatic drugs or steroids until at least six months after diagnosis had significantly higher Health Assessment Questionnaire–Disability Index scores than those who were not treated, after accounting for baseline clinical variables and other factors (eg, smoking status and comorbidities).

However, patients who began treatment within six months of diagnosis had disability scores similar to those of patients who were never initiated on treatment (*Arthritis Rheumatol.* 2017 April 20. doi: 10.1002/art.40090).

"This supports the importance of the 'window of opportunity' construct for treatment, showing that early treatment leads to improved outcomes even into the second decade following symptom onset," wrote James M. Gwinnutt, a PhD candidate at the University of Manchester (England), and his coauthors. "Increased functional disability over time could be due to worse joint damage, and it has been shown that those who receive later treatment have higher radiological scores at follow-up than those treated early."

There were 88 deaths in the early treatment group (55%) during the follow-up pe-

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riod, 99 deaths (39.8%) in the late treatment group, and 78 deaths (40.4%) in the never-treated group.

When the researchers adjusted for disease severity in a comparison of mortality across the groups, they found a trend toward a reduced risk for mortality in patients treated early, compared with those who began treatment later, although this did not reach statistical significance.

However, patients in both the early and late treatment groups showed significantly elevated standardized mortality rates, compared with the general population of Norfolk, while the never-treated group showed slightly, but not significantly, elevated mortality.

Overall, around one-quarter of patients (26.6%) began treatment within six months of the onset of symptoms, 19.9% were started on treatment within six to 12 months, 17.4% started within one to two years, 19% did not start treatment until more than two years after symptom onset, and 43.7% of the cohort never received treatment but still attended follow-up.

Patients who began treatment earlier had worse clinical characteristics than did those who began treatment later, except for tender joint counts and autoantibody status.

Researchers saw an overall decline in median swollen joint count and tender joint count in the first year after baseline, and this remained low throughout the course of the study. Median Health Assessment Questionnaire scores also fell after baseline but then increased steadily from year 2 to year 20, exceeding baseline levels by year 7.

"This paper has two important messages, firstly about the long-term outcome of patients with RA in the modern era treated according to best practice at the time of presentation," the authors wrote, "[and] secondly about the benefit of early treatment which is still apparent into the second decade after symptom onset with respect to functional disability."

An uneven global decline in mortality from RA

Meanwhile, a second study showed that mortality from RA declined globally across 31 countries from 1987 to 2011, according to data from WHO and the UN.

The absolute number of deaths in which RA was registered as the underlying cause declined from 0.12% of all-cause deaths in 1987 to 0.09% of all-cause deaths in 2011 (*Arthritis Rheumatol.* 2017 April 20. doi: 10.1002/art.40091). The mean age-standardized mortality rate declined by 48.2%, from 7.1 per million person-years in 1987-1989 to 3.7 in 2009-2011.

However, there was considerable variation between countries. The greatest reduction was seen in Finland, which had an absolute reduction of 20.6 deaths per million person-years, while Croatia had an increase of 3.7 deaths per million person-years.

Younger people with rheumatoid arthritis showed the greatest reductions in mortality, while those in older age-groups had smaller reductions.

"It has been suggested that changes in the management of RA toward early and aggressive treatment with disease-modifying antirheumatic drugs and subsequent biologic therapies has led to better health status and lower mortality for most people with RA over time," wrote Aliasghar A. Kiadaliri, PhD, of Lund (Sweden) University, and his coauthors.

"These findings alongside aging of the population and fall in mortality may lead to an increase in the number of people with RA. Given that it appears that people with RA are now living longer, increase in burden of RA on health care systems is expected

and policy makers should be made aware to appropriately plan for this anticipated increase."

Disclosures: The first study was supported by Arthritis Research UK. The second study was supported by the Swedish Research Council, Crafoord Foundation, Greta and Johan Kocks Foundation, the Faculty of Medicine at Lund University, and governmental funding of clinical research within Sweden's National Health Service. No conflicts of interest were declared for either paper.

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Target Self-medication of Mood and Anxiety Symptoms

Bruce Jancin

Drinking to alleviate mood or anxiety symptoms is responsible for 12% to 16% of cases of new-onset alcohol use disorder in affected individuals, Jitender Sareen, MD, said at the annual conference of the Anxiety and Depression Association of America. Similarly, the use of prescription or nonprescription drugs to self-medicate these symptoms accounts for 20% of new-onset drug use disorders in this population.

Dr. Sareen, Professor and Head of the Department of Psychiatry at the University of Manitoba in Winnipeg, co-authored two landmark longitudinal epidemiologic studies that support the concept of self-medication as a direct causal mechanism for a commonly observed phenomenon in clinical practice: the high rate of comorbid psychosocial and substance use disorders.

"Questions about self-medication with alcohol or drugs should be included in the assessment of patients with anxiety and mood symptoms, because self-medication is a marker of higher likelihood of psychopathology," Dr. Sareen said. "Psychologic therapies, like cognitive behavioral therapy and dialectical behavior therapy, could prevent onset of substance use disorders by teaching patients emotion regulation skills."

The first longitudinal study included 34,653 nationally representative adults who completed both the initial face-to-face National Epidemiologic Survey on Alcohol and Related Conditions in 2001-2002 and a follow-up survey three years later. During follow-up, 9.7% of subjects developed a new-onset anxiety disorder, 5.9% newly met *DSM-IV* diagnostic criteria for alcohol use disorder, and 2% developed a new-onset drug use disorder.

Among subjects who met the criteria for an anxiety disorder at baseline and also reported self-medication with alcohol, 12.6% developed an incident alcohol use disorder during follow-up. Among those who self-medicated with drugs, 10.4% developed a drug use disorder.

In contrast, among subjects with a baseline anxiety disorder who did not self-medicate at baseline, only 4.7% developed an incident alcohol use disorder and 1.7%, an incident drug use disorder.

For patients with a baseline substance use disorder, self-medication was associated with an increased likelihood of developing social phobia during follow-up (adjusted odds ratio [aOR], 2.13 for alcohol and 3.27 for other drugs). A multivariate logistic regression analysis revealed that, among patients with a baseline anxiety disorder, self-medication with alcohol was associated with an increased risk for incident alcohol use disorder (risk ratio [RR], 2.63) and self-medication with drugs was associated with increased risk for new-onset substance use disorder (RR, 4.99), during follow-up (*Arch Gen Psychiatry*. 2011;68[8]:800-807).

A subsequent analysis focused specifically on drinking to self-medicate mood


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symptoms. Dr. Sareen and colleagues found that self-medication with alcohol was associated with an increased likelihood of new-onset alcohol dependence during follow-up (aOR, 3.1), as well as an increased risk for persistence of alcohol dependence (RR, 3.45). Roughly 12% of all cases of incident alcohol dependence during follow-up were attributed to self-medication with alcohol. The increased risk for new-onset alcohol dependence was observed not only in subjects who met *DSM-IV* criteria for an affective disorder but in those with subthreshold mood symptoms as well (*JAMA Psychiatry*. 2013;70[7]:718-726).

Again, this illustrates drinking to self-medicate mood symptoms as a potential target for preventive interventions. However, no formal studies have been done as yet to confirm the effectiveness of this strategy.

In the third iteration of the National Epidemiologic Survey on Alcohol and Related Conditions (2011-2013), a different group of 36,309 nationally representative adults was interviewed to assess the impact of the *DSM-5* criteria for alcohol use disorder. Using *DSM-5*, 13.9% of the population met criteria for an alcohol use disorder during the past 12 months, and the lifetime prevalence of alcohol use disorder was 29.1%. Fewer than one in five subjects with a lifetime *DSM-5* alcohol use disorder had ever been treated.

In the first national survey, which used *DSM-IV* criteria, the 12-month and lifetime prevalences of alcohol abuse and/or dependence were 8.5% and 30.3%, respectively.

DSM-5 alcohol use disorder was highly comorbid. Both lifetime and 12-month alcohol use disorder were associated with significantly increased likelihood of other substance use disorders, major depression, bipolar I disorder, borderline personality disorder, and antisocial personality disorder.

These data indicate "an urgent need to educate the public and policy makers about alcohol use disorder and its treatment alternatives, to destigmatize the disorder, and to encourage those who cannot reduce their alcohol consumption on their own, despite substantial harm to themselves and others, to seek treatment," the investigators wrote (*JAMA Psychiatry*. 2015;72[8]:757-766).

Disclosures: The surveys were supported by the National Institute on Alcohol Abuse and Alcoholism. Dr. Sareen reported having no financial conflicts of interest.

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Two New Biomarkers for Breast Cancer Show Validity

Mitchel L. Zoler

A pair of breast cancer biomarkers look promising for making better prognosis assessments of selected patients—but will need further documentation of their clinical utility before being accepted into practice, according to Sabine C. Linn, MD, a senior breast cancer oncologist who served as discussant for the studies.

One of the markers is high intratumor heterogeneity of estrogen receptor density, a flag of poor prognosis when heterogeneity is high. The second marker is the phosphorylated signal transducer and activator of transcription (pSTAT) 3, which appeared to link with good prognosis in estrogen receptor–positive breast cancer.

Both markers already appear to have analytic and clinical validity based on two independent reports at a breast cancer conference sponsored by the European Society for Medical Oncology. The data on intratumor estrogen-receptor heterogeneity "is a very intriguing observation. If its validity is confirmed, it would be a very useful assay, with the advantages of being cheap and not needing additional tests" to confirm a poor prognosis, said Dr. Linn, a Professor of Medical Oncology and specialist in molecular pathology at the Netherlands Cancer Institute. The evidence reported for pSTAT3 showed that expression "strongly correlated with disease-free survival" that could potentially serve as a "warning sign before embarking on STAT3 inhibitor studies in the adjuvant setting," she suggested.

The data on intratumor estrogen-receptor heterogeneity came from specimens collected from the low-risk breast cancer patients enrolled in the Stockholm Adjuvant Tamoxifen trial during 1976-1990 (*Acta Oncol*. 2007;46[2]:133-145). Enrolled patients had lymph node–negative disease and primary tumors smaller than 30 mm. During the trial, researchers preserved formalin-fixed tumor specimens in paraffin from 778 patients, which formed the basis for the current study, explained Linda S. Lindström, PhD, a cancer epidemiologist at the Karolinska Institute in Stockholm.

Slides from the specimens were restained for their estrogen receptor content in 2014 and assessed by two independent breast cancer pathologists. They scored the heterogeneity of estrogen receptor distribution as high, medium, or low, and Dr. Lindström and her associates calculated a hazard ratio (HR) for 25-year patient survival when they compared 593 specimens with high or low receptor heterogeneity. They adjusted HRs for several baseline variables, including age, year of breast cancer diagnosis, HER2 status, Ki67 status, tumor grade, tumor size, randomization to tamoxifen or placebo treatment, and other factors.

The analysis showed that women with high intratumor estrogen receptor heterogeneity had nearly twice the rate of long-term breast cancer–specific death, compared with women who had low receptor heterogeneity. A second adjusted analysis that focused on specimens from 336 of these women with luminal A tumors showed that high receptor heterogeneity linked with an HR of 2.4 for long-term cancer-specific death, compared with women with low-heterogeneity tumors.

"Routine clinical assessment of intratumor heterogeneity of estrogen receptor may identify patients at high long-term risk for fatal breast cancer that may potentially change clinical management, especially for patients with luminal A subtype tumors," Dr. Lindström said. "I'd like to see the C statistic; will the prognostic model improve significantly with this added? We need at least two more independent validations."

The second biomarker study used two separate analyses of pSTAT3 expression. The first involved specimens collected from 3,074 patients with luminal breast cancer. Analysis of pSTAT3 gene signature expression showed that the higher expression

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levels were associated with better relapse-free survival during follow-up of up to eight years, reported Amir Sonnenblick, MD, an oncologist at the Sharret Institute of Oncology of Hadassah-Hebrew University Medical Center in Jerusalem.

To confirm and extend this finding, he and his associates used data and specimens collected in the Breast International Group 2-98 phase III trial, which tested the effect of adding docetaxel, either in sequence to or in combination with anthracycline-based adjuvant chemotherapy, in women with node-positive and estrogen receptor–positive breast cancer (*Eur J Cancer*. 2015; 51[12]:1481-1489). The current analysis used 610 tumor specimens from among the 2,173 pathology specimens collected in the study and assessed pSTAT3 protein expression and correlated that with outcomes during a median 10.1-year follow-up. The new pathology review found some level of pSTAT3 in tumor or stroma of 174 (29%) of the 610 specimens examined.

Univariate analysis showed that binary pSTAT3 expression (positive or negative) significantly correlated with 10-year overall survival, with an HR of 0.66 for patients with positive expression compared with those with no pSTAT3 expression, Dr. Sonnenblick said.

"pSTAT3 is associated with improved outcome in estrogen receptor–positive breast cancer," he concluded. "Future trials should take pSTAT3 status into account."

Dr. Linn cautioned that pSTAT3 expression should not be used to identify patients who can forgo chemotherapy, as the gene signature expression analysis showed that, even among patients with high pSTAT3 expression, long-term survival was still less than 90%.

Disclosures: Dr. Lindström and Dr. Sonnenblick had no disclosures. Dr. Linn has been an adviser to AstraZeneca, Cergentis, IBM Health, Novartis, Pfizer, Phillips Health, Roche, and Sanofi.

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Time to Therapy for Gram-positive Bacteremia Reduced From 60 Hours to 4 Hours

Brian Hoyle

Implementation of sample testing using a molecular approach, combined with coordinated and multidisciplinary notification of clinicians, has reduced the time to deliver adequate antibiotic therapy for bacteremia caused by gram-positive cocci, including methicillin-resistant *Staphylococcus aureus* (MRSA), from 60 hours to 4 hours.

"We observed a significant decrease in the time to adequate antibiotics, significant decrease in time to first negative blood culture, and decreased variation in both measures," Michael Tchou, MD, of the Division of Hospital Medicine at Cincinnati Children's Hospital Medical Center (CCHMC), reported at the Pediatric Academic Societies meeting.

The traditional clinical pathway for gram-positive cocci-related infections involves the immediate use of empiric antibiotics, followed by a stepwise process that involves growth of the organisms on blood agar, Gram staining, species identification, and determination of which antibiotics will actually be effective. The intervening period between the empiric and potentially inadequate antibiotics and those that are truly

effective can be 48 hours or longer.

Speeding up the time to delivery of adequate antibiotics is a must, Dr. Tchou emphasized.

CCHMC initiated the use of a multiplex polymerase chain reaction (PCR)–based identification protocol in mid-2013. Multiplex PCR targets specific regions of genetic material. In the protocol, empiric antibiotics are administered. At the same time, multiplex PCR is done. Blood culture and subsequent Gram staining of the bacteria in the colonies that grow are also done. PCR-based species identification and determination of probable antibiotic resistance, which takes about three hours, can be used to shift antibiotic therapy to adequate therapy (defined as the necessary antimicrobial therapy, even if it is still too broad). The growth-based results available the next day help fine-tune treatment.

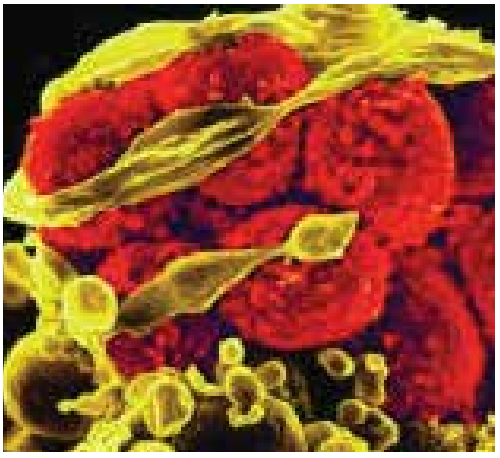
The use of multiplex PCR speeds the time to an "actionable result"—the time to recognize that the empiric antibiotic therapy is not the best, Dr. Tchou said.

At CCHMC, an actionable result is obtained for about one of every 40 cases of bloodstream infection determined to be caused by gram-positive cocci. The delay in switching to adequate antibiotic coverage used to average 60 hours.

In an effort to do better, Dr. Tchou and colleagues set a goal of reducing the time to adequate antibiotic therapy for gram-positive bacteremia from 60 to 12 hours within six months.

The effort required coordination among a multidisciplinary team, a rapid system of clinician notification, and real-time, software-based monitoring of results. In the system, an actionable result triggers a text message to the on-call antibiotic stewardship contact, who in turn notifies the primary care team.

The multidisciplinary system was rolled out first for MRSA. The effort was even more successful than hoped for. Delivery of appropriate antibiotics for MRSA infections dropped from about 60 hours to 13 hours within a few months, with a further decrease to four hours within another few months. Roll out of the initiative to all gram-positive cocci, including coagulase-negative staphylococci, *Streptococcus pyogenes*, *Enterococcus faecalis*, and *E faecium*, similarly achieved the four-hour target within months.



Shown are methicillin-resistant Staphylococcus aureus bacteria.
Courtesy U.S. National Institute of Allergy and Infectious Diseases

And preliminary results not presented by Dr. Tchou indicate an earlier resolution of bacteremia.

Next steps include modifying the decision-support software to allow direct paging of providers instead of using text messages, expanding the antibiotic coverage, and achieving similar improved treatment time for gram-negative bloodstream infections. **CR**

Disclosures: The study was sponsored by Cincinnati Children's Hospital and was not funded. Dr. Tchou reported having no relevant financial disclosures.

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