

# Hospital Medicine

Evidence-Based Information for Hospitalists, [ALERT]  
Intensivists, and Acute Care Physicians

## Follow-up Blood Cultures in Gram-negative Bacteremia — Don't Order Them

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow reports no financial relationships related to this field of study.

**SOURCE:** Canzoneri CN, Akhavan BJ, Tosur Z, et al. Follow-up blood cultures in Gram-negative bacteremia: Are they needed? *Clin Infect Dis* 2017;65:1776-1779.

In a retrospective study conducted at a large hospital in Houston, researchers studied 500 episodes of bacteremia to determine the frequency of follow-up blood cultures (FUBC) and assess risk factors for persistent bacteremia. Of the 500 episodes of bacteremia, 383 (77%) had at least one FUBC drawn. This included 54% of patients with initial bacteremia due to Gram-positive cocci (GPCs), 37% with bacteremia due to Gram-negative rods (GNRs), and 8% with polymicrobial bacteremia. Persistent bacteremia (defined as positive blood culture for the original organism at least 24 hours after the initial blood culture was drawn) was more common in GPC bacteremia (21%) than in polymicrobial (10%) or GNR bacteremia (6%). Duration of bacteremia was similar between groups (2.7-2.9 days). Positive FUBCs were most commonly *Staphylococcus aureus* (31),

coagulase-negative *Staphylococcus* (six), *Enterococcus* (four), *Escherichia coli* (five), and *Klebsiella*, *Serratia*, and *Stenotrophomonas* (one each).

For all patients in the case series, factors shown to be predictive for positive FUBCs included fever on the day the FUBC was drawn, presence of a central catheter, and ESRD on hemodialysis. When broken down by persistent GPC vs. GNR bacteremia, fever, presence of a central catheter, DM, and ESRD on hemodialysis were present for GPC bacteremia, but only the presence of fever at the time the FUBC was drawn was predictive of persistent GNR bacteremia (six of eight patients).

The source of bacteremia was known in 273 (71%) patients who had FUBCs drawn. Only 37 had

**Financial Disclosure:** Hospital Medicine Alert's Physician Editor, Kenneth P. Steinberg, MD, Peer Reviewer Rachael Safyan, MD, Editor Jesse Saffron, Editor Jill Drachenberg, and Editorial Group Manager Terrey L. Hatcher report no relevant relationship related to the material presented in this issue.

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Hospital Medicine Alert,  
ISSN 1931-9037, is published monthly by  
AHC Media, a Relias Learning company,  
111 Corning Road, Suite 250,  
Cary, NC 27518-9238.

GST Registration Number: R128870672.  
Periodicals Postage Paid at Cary, NC, and at  
additional mailing offices.

POSTMASTER: Send address changes to  
Hospital Medicine Alert,  
Relias Learning  
111 Corning Road, Suite 250  
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positive FUBCs. Broken down by source, the rate of positive FUBCs was quite low for most sources (UTI 3%, severe skin infection 6%, intra-abdominal infection 10%, osteomyelitis 0%, but higher for central catheter [34%] and pneumonia [15%]).

## ■ COMMENTARY

At our institution, FUBCs are ordered commonly, and when physicians are questioned about this practice, they are surprised to learn that this is not considered standard of care. This relatively small study goes a long way

toward illuminating that this is not a very helpful practice, especially in patients with GNR bacteremia who are doing well on appropriate antibiotics. (Overall, of the 140 patients with initial GNR bacteremia, it should be emphasized that only eight had positive FUBCs.)

As the authors point out, not only does ordering routine follow-up blood cultures in patients with GNR bacteremia seldom produce helpful information, but common false-positive results can lead to longer length of stay, additional inappropriate antibiotic therapy, and increased healthcare costs. ■

# More ICU Care Does Not Equal Better Survival for Elderly Patients

By Elaine Chen, MD

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Dr. Chen reports no financial relationships relevant to this field of study.

SOURCE: Guidet B, Leblanc G, Simon T, et al. Effect of systematic intensive care unit triage on long-term mortality among critically ill elderly patients in France: A randomized clinical trial. *JAMA* 2017;318:1450-1459.

With an aging population and growing numbers of ICU beds, the question arises as to whether the ICU truly is beneficial for this vulnerable population. To explore this question, a cluster-randomized, clinical trial was designed to determine whether a method of systematic ICU admission in critically ill elderly patients reduced six-month mortality.

This study, ICE-CUB 2, took place in France from 2012-2015. Twenty-four hospitals were each randomized to either the control group or intervention group. In the intervention group, the researchers implemented a program to promote systematic ICU admission. This included a direct conversation between the ED and ICU physicians, bedside evaluation by the ICU physician, and a joint decision regarding admission. Included patients were  $\geq 75$  years of age with a critical condition, preserved functional and nutritional status, and free of active cancer.

The primary outcome assessed was six-month mortality. Secondary outcomes included ICU admission rate, hospital mortality, functional status, and quality of life

at six months. Other secondary outcomes included characteristics of the triage process.

Over a 39-month period, 1,519 patients from 11 hospitals were recruited to the systematic strategy group and 1,518 patients from 13 hospitals were recruited to the standard practice group. The recruitment rate was higher in the systematic strategy group, leading to a shorter inclusion period. The average age was 85 years, and the patients in the systematic group exhibited a higher initial severity of illness.

Regarding the primary outcome, the intervention group demonstrated a slightly higher six-month mortality rate compared to the control group (45% vs. 39%; relative risk [RR], 1.16; 95% confidence interval [CI], 1.07-1.26;  $P < 0.001$ ); the statistical significance did not remain after adjustment for severity of illness (RR, 1.05; 95% CI, 0.96-1.14). Regarding secondary outcomes, the ICU admission rate was higher in the systematic group compared to the standard group (61% vs. 34%; RR, 1.80; 95% CI, 1.66-1.95;  $P < 0.001$ ), and hospital mortality was higher in the systematic strategy

group (30% vs. 21%; RR, 1.39; 95% CI, 1.23-1.57;  $P < 0.001$ ). Comparing patients between the two groups, the systematic group exhibited statistically significant higher severity of illness and more frequent mechanical ventilation. ICU and hospital lengths of stay were not different between the groups, nor was ICU mortality.

This program to promote systematic ICU admission of critically ill elderly patients led to a higher ICU admission rate and increased hospital mortality, but produced no significant effect on six-month mortality, functional status, or physical health-related quality of life.

The authors noted that their patient selection, which excluded very sick patients, may have contributed to lower-than-expected mortality rates. The authors surmised that perhaps the higher in-hospital mortality rate in the systematic strategy group may be related to more frequent withdrawal of life-sustaining therapy.

#### ■ COMMENTARY

Advanced monitoring and aggressive interventions in modern ICUs save many lives. Both ICU beds and usage are increasing. However, ICU care also can be harmful or even futile.<sup>1</sup> Ideal triaging of patients would maximize benefit while optimizing cost. Admission practices to ICUs vary widely: locally among providers (even within a hospital), regionally among hospitals, or more broadly based on location (urban vs. rural, country by country). This large multicenter study protocolized this decision-making process. While defined objective criteria were provided, it remained a clinical decision by the physicians.

The strategy successfully doubled ICU admission rates, yet did not affect long-term outcomes. The only significant outcome was that in-hospital mortality was higher. The authors thoughtfully discussed several strengths and limitations of their study, acknowledging both benefits and challenges because of clustering. Qualitative studies regarding reasons for declining admission in the inter-

vention group or choice of admission in the control group could reveal significant insights into practice.

Study design of this large, randomized trial was reported previously; this study failed to show benefit with increased ICU use in elderly patients.<sup>2</sup> Prior studies, some showing improvement in mortality and others showing no benefit, were observational or retrospective in design.<sup>3-6</sup> For American physicians, who have easier access to ICUs than the French, this study invites more questions: How do we reduce or minimize the harm because of excessive ICU use? How do we systematically monitor and audit our ICU use to optimize benefit? How can we move the question upstream, before ED presentation, to the primary care providers, geriatricians, oncologists, and other referring providers? For now, we should practice thoughtfully, and await further research. ■

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## Implementing Noninvasive Ventilation: If You Build It, They Will Come

By *Richard Kallet, MS, RRT, FCCM*

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Mr. Kallet reports he is a major stockholder in the Asthma & Allergy Prevention Company, and receives grant/research support from Nihon Kohden.

**SOURCE:** Fisher KA, Mazor KM, Goff S, et al. Successful use of noninvasive ventilation in chronic obstructive pulmonary disease. How do high-performing hospitals do it? *Ann Am Thorac Soc* 2017;14:1674-1681.

**T**his study was based on in-depth interviews with 32 “key stakeholders” (15 respiratory care practitioners, 10 physicians, and seven nurses) from

seven institutions recognized as “high performers” in the use of noninvasive ventilation (NIV) to treat acute exacerbations of chronic obstructive pulmonary disease

(AECOPD). The research methodology employed (“positive deviance”) posits that solutions to complex problems can be gleaned from extensive interviews that elucidate strategies and contextual factors from institutions that have overcome barriers to success. Audiotaped interviews were subjected to multiple rounds of thematic analysis, which distilled features essential to success under the rubrics: processes, structural elements, and contextual features.

Identified processes were timely identification of AECOPD patients, early initiation of NIV, and the ability of clinicians to devote the time necessary to ensure sustained compliance with therapy through frequent reassessment. Structural features encompassed what are essentially economic aspects such as the availability of sufficient, appropriate supplies placed in proximity to need (e.g., equipment storage rooms in the ED).

In particular, supplying ventilators specifically designed with NIV capabilities and the availability of a wide variety of mask interfaces both were crucial in ensuring patient comfort and compliance with therapy. Moreover, the allocation of sufficient respiratory care staffing to execute what is an intensive, time-consuming therapy also was critical. Contextual factors included global clinician advocacy, respiratory care practitioner autonomy, interdisciplinary teamwork, and a commitment to continuing education and training. Finally, a systems-level approach was characterized by institutional commitment to NIV as a front-line therapy signified by advocacy for and development of clinician-directed protocols.

#### ■ COMMENTARY

Over the past 40 years, there has been tremendous flux in the structure and delivery of hospital care in terms of economics, regulations, technology, and culture. To be fully appreciated, the effect of these changes must be viewed from the perspective that the practice of medicine is as old as civilization itself. Historically, medicine has been based on a hierarchical structure. This was impressed on me back in the 1970s, when a medical anthropology professor pointedly emphasized that hospitals were the only civilian enterprise in Western culture run on a strict military paradigm.

However, in the mid-1990s an inkling of a paradigm shift began in what the authors described as a “flattening of hierarchy.” In part, this was brought about by societal demands for cost containment through evidence-based care that demonstrated improved patient-centered outcomes.

As a consequence, reimbursement for healthcare has begun to shift slowly from volume-based to quality-

based measures. This has necessitated the development of standardized protocols/guidelines to drive practice and measure outcomes.

One of the results from this confluence of events has been the emergence of respiratory care practitioners as an integral part of the multidisciplinary team. What began in its nascent stage as loading dock workers delivering H cylinders of oxygen to the wards in the late 1940s evolved into a technical specialty coinciding with the advent of critical care in the mid-1960s. By the mid-1980s, the development of microprocessor-controlled ventilators and other sophisticated respiratory care devices moved the profession further, as out of practical necessity it precluded other inundated professions from gaining mastery. However, until very recently, this reality has tended to outpace perceptions within the hospital culture.

Beginning in the mid-1990s, large randomized, controlled trials increasingly demonstrated the efficiency of protocolized care for numerous medical conditions. An overlooked lesson from the successful NHLBI ARDS Network trials was the fact that very complex protocols governing mechanical ventilation and fluid/vasopressor management were executed competently and efficiently by respiratory care practitioners and nurses alike.

As a former ARDSNetwork site coordinator, it was deeply gratifying to witness the enthusiasm with which these bedside professionals responded to this challenge. Similar results have been reported by other large protocolized studies examining different aspects of care, such as weaning and sedation practices and prone positioning for acute respiratory distress syndrome.

In this study, Fisher et al affirmed that that giving allied health professions autonomy to execute care within well-structured, supervised protocols/guidelines is an efficient solution to many of the current obstacles in providing patient care in an increasingly fractured environment. However, there was not enough emphasis in the Fisher et al study on the indispensable need for physician and administrative leadership to give their full-throated support to this endeavor. As alluded to previously, any expectation that a culturally ancient and hierarchical entity will undergo fundamental transformation readily within a few brief decades would be naïve.

It will take dogged perseverance by those in leadership positions to foster this emerging care paradigm and guarantee its success. To paraphrase an old movie cliché: “If you build it, they will come.” The study by Fisher et al is a very important contribution that gratifyingly highlights the contributions of one particular profession still struggling for its place at the table. ■

# Stroke Alert

By Matthew E. Fink, MD

## Thrombectomy Is Effective Up to 24

### Hours After Stroke – the DAWN Trial

**SOURCE:** Nogueira RG, Jadhav AP, Haussen DC, et al; for the DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2017; Nov. 11. doi: 10.1056/NEJMoa1706442. [Epub ahead of print].

**A**t the International Stroke Conference in 2015, five separate randomized trials were reported and simultaneously published that definitively showed that endovascular thrombectomy with a stent retriever had a clinical benefit when it was performed within six hours after onset of stroke symptoms, with diminishing benefit as the interval between time of onset and thrombectomy increased. In the recently published DAWN trial, researchers studied a group of patients who had onset of symptoms more than six hours and up to 24 hours before enrollment and had a mismatch between neurological deficit and infarct size, using a novel imaging approach to determining mismatch. Many of these patients were so-called “wakeup strokes.” Patients were enrolled and divided into two groups, < 80 years or ≥ 80 years of age, and were assigned randomly to thrombectomy plus standard care or to standard care alone. The primary endpoints were the mean score for disability on a utility-weighted modified-Rankin scale, which ranges from 0 (dead) to 10 (no symptoms or disability), and the rate of functional independence using the modified-Rankin scale at 90 days.

Patients were eligible for inclusion if they had evidence of occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both,

on either CT angiography or MR angiography. In addition, they had to show a mismatch between the severity of the clinical deficit and infarct volume. In the group of patients ≥ 80 years of age, a score of 10 or higher on the NIH stroke scale and infarct volume of < 21 mL indicated mismatch. In those < 80 years of age, mismatch was defined as a score of 10 or higher on the NIH stroke scale, and an infarct volume of < 31 mL. Infarct volume was measured by either diffusion-weighted MRI or perfusion CT.

A total of 206 patients were enrolled; 107 were assigned to the thrombectomy group and 99 to the control group. At 31 months, enrollment in the trial was stopped because a pre-specified interim analysis demonstrated significant differences in outcome between the groups. In the thrombectomy group, the utility-weighted modified Rankin scale at 90 days was 5.5 compared to 3.4 in the control group, with high statistical significance. The rate of functional independence at 90 days was 49% in the thrombectomy group compared with 13% in the control group, also highly statistically significant. There was no significant difference in 90-day mortality (19% vs. 18%), and the rate of symptomatic hemorrhage did not differ significantly between the groups (6% in the thrombectomy group and 3% in the control group).

In conclusion, among a group of ischemic stroke patients last known to be well six to 24 hours earlier and who had a mismatch between clinical deficit and infarct size, outcomes regarding disability and functional independence were better if treated with mechanical thrombectomy, rather than standard care alone. ■

## Rehabilitation From Neurological Insults: The Role of Music-based Interventions

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

**SOURCE:** Sihvonen AJ, et al. Music-based interventions in neurological rehabilitation. *Lancet Neurol* 2017; 16:648-660.

**M**usic is an integral part of the human experience, existing in cultures and civilizations throughout history. Although the purpose, meaning, and significance may vary over time, the universal pull of

rhythm allows music to assist in crossing language and other psychosocial barriers. Interest in incorporating music into medical treatment is equally universal. An early case report from Sweden in 1745,

“On a mute who can sing,” describes a farmer’s son who developed aphasia post-stroke but retained the ability to sing familiar tunes.<sup>1</sup> This may be the first documented report suggesting that the ability to speak words and to sing words are directed by different areas of the brain. As our awareness of the effect of music on the brain has evolved, it is not surprising that interest in studies investigating musical interventions have blossomed.<sup>2</sup>

Known to improve connectivity of neurons, listening to music reduces the level of analgesics and enhances patient satisfaction in postsurgical settings.<sup>3</sup> Active participation in a musical activity appears to stimulate grey and white matter changes and increase neural plasticity.<sup>4</sup> Therefore, the use of music-based interventions is a natural fit for areas in which cortical stimulation is essential for progress, such as in the recovery and treatment of neurological disorders.

Noting that the financial and medical burden of neurological disorders often lie in recovery and rehabilitation, Sihvonen et al reviewed and consolidated knowledge of the effect of music-based interventions in rehabilitation of specific disorders, including stroke, dementia, Parkinson’s disease, multiple sclerosis, and epilepsy. Within these broad categories, the authors identified areas of specific impact, such as cognitive rehabilitation, speech post-stroke, or gait in Parkinson’s disease.

The music-based interventions and outcomes in the included studies are quite diverse and cover a range of interventions, including traditional music therapy, rhythmic auditory stimulation (synchronizing movements to rhythm), and music-supported therapy (playing musical instruments usually to help with rehabilitation of gross and fine movements). One newer modality in music-supported therapy involves transforming movement into sound as part of music sonification therapy. For example, a post-stroke patient is encouraged to move an affected arm as a technician attaches sound to position in space, thus substituting rhythmic melodies for impaired proprioception. In this manner, a patient can relearn to eat by “playing” specific sounds or tunes while changing arm position (rather than relying on an impacted internal sense of position in space).<sup>5</sup>

One challenge with such diversity of interventions and outcomes (as well as different disease states) is the meaningful comparison of results. Sihvonen et al used Cohen’s *d* value to measure, rate, and compare the effect size of specific outcomes. Cohen’s *d* is a common way to measure effect size in meta-analytic studies. An effect size is defined as small if  $d = 0.2$

(may not be a meaningful effect and not easily discernible), medium if  $d = 0.5$ , and large if  $d \geq 0.8$ .<sup>6</sup> Control group protocol varied from study to study.

#### Selected Results

**Stroke:** Sixteen randomized, controlled trials (RCTs) were included in this category. Outcomes included motor movements, language improvements, cognitive functions, mood, and quality of life. Two studies show no significant difference between intervention and control groups. In both studies, the control group used a form of sound or other therapy. Sample sizes ranged from 20 to 92.

**Dementia:** The authors reviewed 17 RCTs in this category. Most involved music-based therapies and the effect on neuropsychiatric and behavioral symptoms (anxiety, depression, agitation, cognition, and quality of life predominate.) Sample sizes ranged from 18 to 100 participants. Four studies showed no significant difference between the intervention and control groups. It is noteworthy that most of the studies showing cognitive improvement in dementia were restricted to patients with mild forms of this disorder. Two of the RCTs that did not demonstrate an effect from music-based interventions on mood used control groups with active non-music interventions rather than standard care.

**Parkinson’s Disease, Multiple Sclerosis, and Epilepsy:** The authors of five RCTs in this review investigated music-based interventions in Parkinson’s disease, primarily looking at the effect on motor symptoms of this degenerative disorder as well as evaluating quality of life and social parameters. All sample sizes were small, with only one study involving more than 50 participants. Dancing clearly had the most effect on motor symptoms in the reviewed studies, helping with balance, stride length, and general mobility.

Only two RCTs included in this study involved music-based interventions in multiple sclerosis, one of the more common neurological disorders occurring in the young adult population. Treatment has been proposed to decrease or prevent flare-ups of new episodes. Neither study included more than 20 participants; results are inconclusive and, according to the study group, allow no firm recommendations.

One RCT was included for epilepsy. These authors looked at stimulation of the cortex via music as a mechanism to reduce epileptiform activity. Classical music was played every night for a year to 73 participants; the control group received no intervention. Seizure frequency in the active group decreased by 17% ( $P = 0.14$ ) during the treatment phase and by 16% one-year post treatment.

## ■ COMMENTARY

Given the widespread access and relatively inexpensive availability of music, the use of music-based interventions in the complex care of patients with neurological disorders is an attractive proposition. In fact, for many caregivers, the informal use of music during treatments and in daily life may be less strategic and more intuitive. This large-scale review study brings promising direction to the field; understanding the effect of specific musical interventions on specified outcomes could and should lead to a more targeted and efficacious approach.

Understanding the effect but also the mechanism of action of these musical interventions is important. At this point, explanations remain speculative — the process is not yet well-delineated. Sihvonen et al offered several possible etiologies that could explain the results presented in the reviewed studies. These are based largely on what is known about the effect of music on the healthy brain.

Three proposed mechanisms were presented: enhancement of neural activation, cerebral blood flow, and neuroplasticity; activation of reward centers; and/or activation of spared neural networks.

Modern medical innovations and imaging studies have confirmed findings from early observational studies (such as a “mute who could sing” noted earlier.) The sparing of music abilities despite widespread speech and language loss led to early conclusions that speaking, language, and music may involve different areas of the brain. We now know that singing, for example, involves bilateral and more extensive areas of the brain than speaking. This allows intervention aimed at relatively healthy portions of the brain post-insult. Familiar tunes activate the anterior and medial prefrontal cortex — areas that tend to be spared from rapid degeneration in Alzheimer’s disease and may help explain why singing is often preserved in these patients.<sup>7</sup>

Although work remains to be done regarding understanding the full etiology and mechanism of music-based interventions, gaps remain regarding what we know about when the interventions work best and which are most effective.

Studies that clearly spell out protocol, including presence or absence of speech therapist and type of music applied, are necessary to make firm recommendations. Looking for publication bias among the published studies is important; replication of the studies in a methodical manner is essential to bring legitimacy and further develop this field.

Future direction in use of music-based interventions most likely will look at the length of time interventions show an effect, the need to reinforce, as well as any relationship between response to music-based interventions and exposure or involvement in music during premorbid years. A not well-studied but hidden benefit of music-based interventions in these neurological disorders may be the positive effect on a caregiver. A caregiver may receive some of the same mood benefits from the music as the patient, a potentially far-reaching intervention given what we know about the stress involved in caring for patients with neurological disorders.<sup>8</sup> The development of effective music-based interventions implemented by a caregiver within a home setting provides numerous benefits from economic, logistical, and health perspectives.

There remains enough evidence to promote the use of music-based interventions during rehabilitation and recovery of motor deficits post-stroke, in mobility in Parkinson’s disease, and in treatment of aphasia post-stroke. In dementia, the use of music-based interventions may help with cognitive improvements in early stages of the disease. Although there are mixed results regarding an effect on mood and agitation in dementia and post-stroke, there is no recognizable harm. The results of the investigations of music-based interventions in multiple sclerosis and in epilepsy are inconclusive, but promising preliminary results show exciting potential. Sharing this information with patients and caregivers allows the provider to help shape an innovative and comprehensive treatment plan for rehabilitation from devastating neurologic insults.

The specifics of such a plan will vary not only with patient preference and condition, but also with practical considerations, such as availability of music therapists, caregiver attitudes, and physical limitations such as hearing impairment. At the least, providers can offer the suggestion to add music to everyday routines, all the while remaining actively vigilant in a search for more tailored and accessible interventions appropriate for each unique individual. ■

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### CME QUESTIONS

**1. Which of the following is true of adapting a systematic strategy to promote ICU admission for the elderly?**

- a. Both emergency and intensive care physicians reported improved job satisfaction.
- b. Increased ICU admission rates improved nurses' job satisfaction.
- c. Increased severity of illness is associated with higher ICU admission rates.
- d. Increased ICU admission rates may not change long-term outcomes.

**2. The DAWN trial showed that mechanical thrombectomy results in better functional outcomes after ischemic stroke than does intravenous thrombolysis.**

- a. True
- b. False

**3. Which of the following is true regarding music-based interventions in neurological rehabilitation?**

- a. Although evidence of efficacy is clear post-stroke and in early stages of dementia, music may be too stimulating for patients with epilepsy and care should be taken to avoid music during sleep in these patients.
- b. Music-based interventions show evidence of efficacy post-stroke for help with motor deficits and aphasia and in improvement of motor deficits in Parkinson's disease.
- c. Music-based interventions show evidence of efficacy post-stroke with motor deficits and aphasia as long as a musical therapist is involved for at least 50% of the treatment period (three times weekly, up to 10 weeks post-infarct).
- d. In Parkinson's disease patients, motor deficits improved with exposure to familiar songs for 20-30 minutes four times weekly.

### CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and;
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems.

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