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INSIDE

Fidaxomicin after Vancomycin for Patients with Multiple *C. difficile* Recurrences

ABSTRACT & COMMENTARY

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Dr. Watkins reports no financial relationships in this field of study.

This article originally appeared in the November 2012 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, FIDSA, and peer reviewed by Timothy Jenkins, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University, and Dr. Jenkins is Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck, and Dr. Jenkins reports no financial relationships relevant to this field of study.*

Synopsis: *Three patients with multiple recurrences of* C. difficile *infection who were on prolonged maintenance therapy with low-dose vancomycin were treated with a standard course of fidaxomicin. Two had no further recurrences, and one recurred three months later following a course of levofloxacin.*

Source: Johnson S, Gerding DN. Fidaxomicin 'Chaser' Regimen following Vancomycin for Patients with Multiple *C. difficile* Recurrences. *Clin Infect Dis* 2012; Sep 28. [Epub ahead of print]

Recurrent *C. difficile* infection (CDI) is a challenging condition to manage. Current guidelines estimate that 25% of patients treated for CDI experience at least 1 additional episode, with those aged 65 years or greater at highest risk.[1] Recurrences are thought to occur either from relapse by the original strain through germination of residual spores, or re-infection in patients who remained susceptible and are

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exposed to new strains. Possible treatment options for recurrent CDI include oral vancomycin given in tapering doses (usually over six weeks), rifaximin, nitazoxanide, intravenous immunoglobulin, and fecal transplantation. Fortunately, most patients are eventually cured. However, some experience multiple recurrences, for which treatment data are limited.

Fidaxomicin, a macrolide antibacterial, was approved in May 2011 for treatment of CDI. Drs. Johnson and Gerding have reported their experience using fidaxomicin to treat three patients with multiple recurrences of CDI, a male aged 67 years, a female aged 80 years, and a female aged 32 years. All three had received tapering courses of vancomycin, followed by maintenance with low-dose vancomycin for five to six months. One of them had been given two rifaximin 'chasers' after vancomycin tapers and initially did well, but eventually developed mucous stools and abdominal cramps necessitating another course of oral vancomycin. One patient also received intravenous immunoglobulin. After a 10-day course of fidaxomicin, two of the patients have had no CDI recurrences to date. The third did well until receiving a 3-day course of levofloxacin for a urinary tract infection. One week later a symptomatic recurrence developed. The authors did not describe how this was managed.

■ COMMENTARY

While this was a very small (n = 3), nonrandomized interventional study, fidaxomicin looks promising for multiple recurrences of CDI. While the exact mechanism for reducing recurrences is not known, one possible explanation is that the drug produces an inhibitory effect on sporulation. This was shown in a study sponsored by the drug manufacturer wherein fidaxomicin inhibited the specific sporulation genes spoIIID and spoIIR.[2] Results from two phase three trials, OPT-80-003 and OPT-80-004, showed fidaxomicin was noninferior to vancomycin for curing CDI and superior for reducing CDI recurrences.[3] Fidaxomicin reduced persistent diarrhea, recurrence, or death by 40% (95% confidence interval, 26%-51%; P < .0001) compared with vancomycin through day 40. The novel hypothesis that fidaxomicin might be effective for multiple recurrences needs to be tested by a large, randomized clinical trial. Moreover, the efficacy of combination therapy with fidaxomicin and a second agent (e.g. rifaximin) is not known. The combination of tigecycline and rifaximin was recently reported to successfully cure a patient with recurrent refractory CDI.[4]

Johnson and Gerding did not determine the strain of *C. difficile* causing their patient's infections. In the clinical trials that led to the drugs approval, sustained response was not seen in the sub-group of patients infected with the *C. difficile* NAP1/B1/027 strain. While this could potentially be the "Achilles heel" of fidaxomicin, the cure rates for the NAP1/B1/027 strain have been similar to those from vancomycin. Furthermore, it would have been interesting to know whether the patients in this study had co-morbid illnesses, particularly those that lead to immune compromise. For instance, a defect in immune response to toxin A has been associated with recurrences.[1] Finally, fidaxomicin is expensive (like oral vancomycin) and its cost-effectiveness remains to be elucidated. ■

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Pediatric-Specific Antibiograms Improve Empiric Drug Selection

ABSTRACT & COMMENTARY

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Dr. Jenson reports no financial relationships in this field of study.

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Alert. *It was edited by Stan Deresinski, MD, FACP, FIDSA, and peer reviewed by Timothy Jenkins, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University, and Dr. Jenkins is Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck, and Dr. Jenkins reports no financial relationships relevant to this field of study.*

Synopsis: *Knowledge of pediatric-specific antimicrobial susceptibility data improves prescribing selections of empiric antibiotic treatment. Providers should advocate for availability of pediatric-specific antimicrobial susceptibility data wherever practical.*

Source: Boggan JC, Navar-Boggan AM, Jhaveri R. Pediatric-specific antimicrobial susceptibility data and empiric antibiotic selection. *Pediatrics* 2012;130:e615-e622.

At Duke University Health System, a tertiary-care medical center that has traditionally provided aggregated antimicrobial susceptibility data from both adult and pediatric isolates, antibiograms for *Escherichia coli* isolates from children ≤12 years of age from July 2009 to September 2010 were developed and compared with antibiograms that combined adult and pediatric data. A total of 375 pediatric isolates were obtained from 327 patients. *E. coli* isolates from pediatric patients were more likely to be resistant to amoxicillin, amikacin and TMP-SMX and less likely be resistant to amoxicillin-clavulanate and ciprofloxacin then *E. coli* isolates from all age groups (P<0.0005).

A case-based survey of pediatric providers using two clinical vignettes — a three-month-old infant and a 12-year old-old child — with probable urinary tract infection was used to determine the impact of availability of pediatric-specific data on antibiotic selection. Providers responded to the clinical vignette survey under three circumstances: first with no antibiotic susceptibility data, then with aggregated pediatric and adult susceptibility data, and finally with pediatric-specific susceptibility data. Surveys were completed by 26 of 43 (61%) attending pediatricians and 49 of 92 (53%) pediatrics or medicine-pediatrics residents.

When no data was provided for the case of the 3-month-old, only 68.6% of providers selected an antibiotic with ≥80% in vitro efficacy against *E. coli*. This increased to 82.2% (P=0.08) when aggregated data was provided, and to 92.5% (P<0.01 compared to no data provided) when pediatric-specific data was provided. When pediatric-specific data was presented, providers were more likely to choose amoxicillin-clavulanate and less likely to choose TMP-SMX.

When no data was provided for the case of the 12-year-old, only 32.4% of providers selected an antibiotic with ≥ 80% in vitro efficacy against *E. coli*. This increased to 57.3% (P<0.01) when aggregated data was provided, and to 79.4% (P=0.01 compared to providing aggregated data) when pediatric-specific data was provided.

■ COMMENTARY

Antimicrobial susceptibilities often differ significantly across the age spectrum as well as by the site of care (e.g., inpatient vs. outpatient). This study included a survey using case vignettes that demonstrated that knowledge of pediatric-specific data favorably altered provider empiric antibiotic selection.

Optimal empiric antibiotic selection in children should be based on age-specific antimicrobial susceptibility data, wherever possible, rather than aggregated data that combines pediatric and adult data. This study demonstrates that knowledge of pediatric antibiograms is an effective systematic step that facilitate providers choosing successful empiric antibiotic therapy in children. This should also minimize the adverse effects of antimicrobial use.

In many circumstances, there is minimal incremental work for the microbiology laboratory to report pediatric-specific data but significant benefit to optimal empiric antibiotic selection for children. Aggregating pediatric and adult data will likely continue to be necessary for infrequent isolates. For common isolates such as *E. coli*, pediatric providers should advocate with directors of clinical microbiology laboratories to provide availability of pediatric-specific antimicrobial susceptibility data wherever practical. ■

Safety of High- vs. Moderate-Intensity Exercise for Cardiac Rehabilitation

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

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This article originally appeared in the November 2012 issue of Clinical Cardiology Alert. *It was peer reviewed by Ethan Weiss, MD, Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Crawford reports no financial relationships relevant to this field of study, and Dr. Weiss is a scientific advisory board member for Bionovo.*

Source: Rognmo O, et al. Cardiovascular risk of high- versus moderate-intensity aerobic exercise in coronary heart disease patients. *Circulation* 2012; 126:1436-1440.

Current guidelines recommend cardiac rehabilitation using moderate exercise programs for most ischemic heart disease (IHD) patients. Also, studies have shown that the intensity of exercise is directly related to the cardioprotective effects. However, there is concern that high-intensity exercise may be dangerous in IHD patients. Thus, these investigators from Norway studied almost 5000 IHD patients in cardiac rehabilitation units that employed both high-intensity interval exercise and moderate-intensity continuous exercise training sessions. High-

intensity exercise was defined as achieving > 85% of maximum predicted heart rate (mpHR) at intervals and moderate as 60-70% of mpHR continuously. The sessions lasted 1 hour and the patients underwent an average of 37 sessions. The primary outcome measure was cardiac arrest or acute myocardial infarction (MI) during or within 1 hour after a session. There were > 129,000 moderate-intensity sessions and > 46,000 high-intensity sessions. There were two non-fatal cardiac arrests during high-intensity exercise and one fatal cardiac arrest in the moderate group. There were no MIs. The authors concluded that both types of exercise training are associated with a low incidence of events and that the presumed benefits of high-intensity exercise training outweigh these risks.

■ **COMMENTARY**

This study is in agreement with other studies of cardiac rehabilitation that showed very low event rates. What distinguishes this study is the use of high-intensity exercise in some of the patients. In their protocol, after a warm-up period, high-intensity exercise was done for 4 minutes and then the patients did low-level exercise until they were symptomatically recovered and were at 50-70% mpHR. This cycle was repeated for almost an hour ending with a cool-down, low-exercise period. The patients were carefully selected clinically and by formal exercise testing. Those with symptoms or signs of ischemia were excluded. Also, these were not all post-MI patients; only 7% were post-MI. Most were post revascularization patients. Thus, this was a low-risk group.

The major limitation of this study was that it was not randomized. However, given the low event rate observed, they estimated that for a randomized trial to show any difference in the two levels of exercise, more than 10,000 patients would be required in each group. Previous randomized trials were all underpowered, and observational studies have inherent biases. Thus, the issue of vigorous vs. moderate exercise for cardiac rehabilitation remains somewhat controversial, especially in post-MI patients. My take is that in carefully selected patients, in a supervised program, vigorous interval exercise is safe. However, if patients are doing their own rehabilitation at home or in their gym, then I recommend they stick to moderate exertion. ■

Multidisciplinary Tracheostomy Teams Shorten Time to Decannulation and Increase Speaking Valve Use

ABSTRACT & COMMENTARY

By Eric C. Walter, MD, MSc

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This article originally appeared in the November 2012 issue of Critical Care Alert. *It was edited by David J. Pierson, MD, and peer reviewed by William Thompson, MD. Dr. Pierson is Professor Emeritus, Pulmonary and Critical Care Medicine, University of Washington, Seattle, and Dr. Thompson is Associate Professor of Medicine, University of Washington, Seattle. Drs. Pierson and Thompson report no financial relationships relevant to this field of study.*

Synopsis: *This systematic review and meta-analysis finds that the implementation of multidisciplinary tracheostomy teams leads to significant improvements in time to decannulation and in speaking valve use but not in ICU or hospital length of stay. The quality of the evidence was low.*

Source: Speed L, Harding K. Tracheostomy teams reduce total tracheostomy time and increase speaking valve use: A systematic review and meta-analysis. *J Crit Care* 2012; Aug 27. [Epub ahead of print.]

This systematic review and meta-analysis reviewed studies evaluating the implementation of multidisciplinary tracheostomy teams in acute care hospitals. Potential studies identified and independently reviewed for inclusion criteria related to population studied, intervention, outcomes, and methodology. The population studied included patients with a temporary tracheostomy or undergoing tracheostomy weaning. Studies of patients with tracheostomies related to structural abnormalities of the trachea or with permanent tracheostomy were excluded. The intervention team must have been multidisciplinary and have included at least two health professionals, including one allied health professional (i.e., speech pathologist, physical therapist, or respiratory therapist). Teams comprised of only medicine, or medicine and nursing, were excluded. Seven studies met inclusion criteria. Study quality was judged to be medium to low as all were observational, with a pre-post design, and there were no randomized controlled trials.

The most common outcome measured was time to decannulation, reported in six of seven studies. Sufficient data were reported from four of these studies to perform a meta-analysis. Tracheostomy teams were associated with a reduction in time to decannulation (mean difference 8 days; 95% confidence interval, -6 to -11; $P < 0.01$). Three of the seven studies reported on speaking valve use and all reported increased use from about one-third or less to two-thirds or more of patients using speaking valves. Because a measure of variability was not available for this outcome, meta-analysis could not be performed. Meta-analysis of three studies that reported hospital length of stay (LOS) revealed a decrease in hospital LOS although the result was not statistically significant. A non-significant reduction in ICU LOS was reported in three studies. Insufficient data were available to perform meta-analysis.

■ **COMMENTARY**

The quality of any meta-analysis is directly related to the quality of included studies. Unfortunately, it has been historically difficult to obtain high-quality data with respect to tracheostomy in critically ill patients. Tracheostomies are performed on only a minority of critically ill patients making it difficult for

any single institution to report outcomes on large numbers of patients, and strong differences of opinion have made multicenter studies challenging. Therefore, despite low-quality studies available for inclusion, meta-analyses such as this study provide useful information for practicing clinicians.

Strengths of this study include careful selection criteria and clinically relevant outcome measures. The authors showed that the introduction of multidisciplinary tracheostomy teams was associated with a statistically significant reduction in time to decannulation. This had been reported in five of the six studies, but small sample sizes limited the ability to report statistically significant outcomes. Tracheostomy teams also appeared to be associated with a greater percentage of patients using a speaking valve. It is not surprising that tracheostomy teams were not associated with a significant reduction in ICU or hospital LOS. LOS is affected by a host of variables, including illness type and severity, a hospital's ability to care for patients with tracheostomies outside of the ICU, and disposition options for these patients. Nevertheless, a shorter time to decannulation and greater use of speaking valves should be highly valued outcomes to both patients and clinicians and argue in support of tracheostomy teams.

However, limitations of this meta-analysis and of the primary studies must be considered. Pre-post intervention studies are considered low grade for valid reasons. A number of changes may occur following an intervention, such as the implementation of a tracheostomy team that may explain the observed outcome. For example, over time improved adherence to low tidal volume ventilation recommendations may decrease lung injury leading to decreased need for long-term tracheostomies.

In summary, the implementation of a multidisciplinary tracheostomy team was associated with a reduction in time to decannulation and an improvement in speaking valve use among critically ill patients with a tracheostomy. While the quality of included studies was low, the findings were generally consistent across studies. The importance of tracheostomy teams may become even more apparent in the future with the growth of percutaneous tracheostomy. As more practitioners perform this procedure, deciding who will follow, and how patients will be followed, will become more important. It makes sense that a dedicated tracheostomy team may help standardize this care and improve outcomes. ■

What HbA1c for the Very Elderly?

ABSTRACT & COMMENTARY

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This article originally appeared in the October 15, 2012, issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Adjunct Clinical Professor, University of North Carolina, Chapel Hill, and Dr. Roberts is Assistant Clinical Professor of Medicine, Albert Einstein College of Medicine, New York, NY. Dr. Brunton serves on the advisory board for Lilly, Boehringer Ingelheim, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Lilly, Kowa, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

Synopsis: *In a nursing home-eligible population with a mean age of 80, those with a HbA1c between 8% and 8.9% had less functional decline than those with a HbA1c of 7% to 7.9%.*

Source: Yau CK, et al. Glycosylated hemoglobin and functional decline in community-dwelling nursing home-eligible elderly adults with diabetes mellitus. *J Am Geriatr Soc* 2012;60:1215-1221.

The dangers of hypoglycemia are being appreciated in this era of tight control of diabetes. Efforts to achieve near normal blood sugars have become standard therapy, but when insulin is being used, episodes of hypoglycemia are more common in tightly controlled patients. We have recently appreciated the dangers of hypoglycemia in hospitalized patients and know that blood sugars in the range of 140-180 mg/dL are better than lower levels.[1]

Cognitive function in the elderly is fragile and hypoglycemia is especially dangerous in this group. It is estimated that 40% of persons older than age 80 have diabetes.[2] Since diabetes in younger adults would be expected to reduce life expectancy below the average, those with diabetes older than age 80 are a different group and in general should be treated differently.

This group of investigators in San Francisco studied 357 elders with diabetes living in the On Lok Lifeways community for 2 years. The average age of these seniors was 80. Fifty percent (185) were taking insulin. All participants were evaluated every 6 months for functional status and control of their diabetes. Over the 2 years, 75% experienced functional decline or death. A higher HbA1c of 8-8.9% was associated with a lower likelihood of functional decline or death than those with a HbA1c of 7-7.9% (relative risk 0.88).

■ COMMENTARY

Tight control of diabetes has become the standard of care for a new generation of physicians. Being in practice for more than 30 years, I remember when an HbA1c level of 8% was considered good control. Tighter control of diabetes has certainly had its benefits in reduced cardiovascular complications and infections, but like most things in medicine and life, intervention is a double-edged sword.

There is a paradox with tight control of diabetes. When aggressive lifestyle management is used, reducing body fat and even reversing the diabetes, all the outcomes are good. However, when insulin and other agents that cause hypoglycemia are used, tight control results in an increased risk of hypoglycemic episodes, a real danger for brain function.

This study is consistent with other emerging data that tight

control of the advanced elderly with diabetes, especially using insulin, may be harmful. I regard my elderly patients older than 80 years with diabetes a different group from other diabetes patients and am much more relaxed with their treatment. They should be excluded from quality metrics that look at the average control of diabetes in a practice with an expected target of 7%. The American Geriatrics Society's current recommendation is for a HbA1c of 8% or less in patients with a limited life expectancy. This recommendation appears to be too low and is likely to be revised upward. ■

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Fungal meningitis and arthritis from epidural, paraspinal and intra-articular injections with contaminated corticosteroid. Early status.

ABSTRACT & COMMENTARY

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This article originally appeared in the November 2012 issue of Infectious Disease Alert. *It was peer reviewed by Timothy Jenkins, MD. Dr. Jenkins is Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck, and Dr. Jenkins reports no financial relationships relevant to this field of study.*

An investigation initiated after a clinician reported to the Tennessee Department of Health on Sept. 18, 2012, the case of a patient who developed meningitis due to *Aspergillus fumigatus* after having received an epidural corticosteroid injection at an ambulatory surgical center quickly identified a number of other suspect cases.[1] By September 27, another 7 patients in Tennessee as well as one in North Carolina who developed meningitis after epidural or paraspinal steroid injection had been identified, but in each case cerebrospinal fluid (CSF) cultures were apparently negative. Each of the injections had utilized a preservative-free solution of methylprednisolone acetate from one of 3 lots that had been compounded from at the New England Compounding Center (NECC). As of October 17, a continuing multistate investigation found that the number of identified cases was approaching 300, with 47 of these having laboratory-confirmed fungal meningitis. By October 22, there were 23 deaths reported, 9 of them in Tennessee. Some presented with basilar stroke rather than with a meningitis syndrome. In addition, "septic" inflammatory arthritis has been reported in 3 patients who had received intra-articular injections of the implicated product.

NECC voluntarily recalled the implicated lots, approximately 17,500 vials of which had been distributed to 75 facilities in 23 states, on September 26 and by October 6th expanded the recall to include all NECC products manufactured since Jan. 1, 2012. A total of almost 14,000 individuals were identified as possibly having been exposed and up to 97% have been notified.

Cases have been categorized as follows (all require that onset followed receipt of an injection of NECC-compounded methylprednisolone acetate after May 21):

• Fungal meningitis or nonbacterial and nonviral meningitis of subacute onset.

• Basilar stroke following epidural injection in a person from whom no CSF specimen was obtained.

• Spinal osteomyelitis or epidural abscess at the site of injection following epidural or sacroiliac injection.

• Septic arthritis or osteomyelitis of a peripheral joint (e.g., knee).

As of October 10, 12 (9%) of 137 patients from 10 states for whom information was available had died. Sufficient additional data to allow categorization was available for 70 of the 137: 64 (91%) had meningitis, 2 (3%) had basilar stroke without CSF examination, 2 (3%) had an epidural abscess or osteomyelitis, and 2 (3%) had both meningitis and epidural abscess or osteomyelitis. These 70 patients ranged in age from 23 to 91 years and 69% were women. At presentation, 81% complained of headache, 34% were febrile, 30% complained of nausea, and 10% had photophobia; 11% reported having fallen. Physical findings indicative of meningeal irritation were identified in only 14% while subtle gait disturbances were noted in 4%. The median time from injection to onset of symptoms for 25 patients who received a single steroid injection was 16 days (range, 4-42 days).

CSF white blood cell counts ranged from 13-15,400/mm3 (median, 1299/mm3) with neutrophilic predominance. CSF glucose ranged from 11-121 mg/dl (median, 42 mg/dl) while the range of protein concentrations was 45-588 mg/dl (median, 129 mg/dl). Laboratory confirmation of fungal infection was achieved in 47 patients as of October 17. Only the index case was due to *A. fumigatus*. Cladosporium was identified in one case, while the remaining 45 infections were caused by *Exserohilum rostratum*. Exserohilum as well as other fungi have been recovered from vials in the implicated lots.

The index case was a man in his 50s who presented 4 weeks after lumbar epidural injections with an 8-day history of headache and neck pain.[2] His CSF protein concentration was 147 mg/dl, glucose 31 mg/dl and white blood cell count of 2304 cells/mm3 (72% neutrophils). He failed empiric antibacterial therapy and subsequent MRI of the brain and spinal cord showed men-

ingeal enhancement and ventriculitis and a <1 cm fluid collection at L4-L5. CSF parameters were worse and after some initial improvement he had neurological deterioration at which time a CSF culture was found to be growing *Aspergillus fumigatus* and he was given voriconazole as well as liposomal amphotericin B (which had been initiated on the previous day). Retrospective analysis found that galactomannan antigen testing was positive on all CSF samples. Repeat MRI demonstrated midbrain and cerebellar infarcts. He then developed intraventricular and subarachnoid hemorrhage with worsening hydrocephalus and died.

Lyons and colleagues have described the cases of exserohilum infection in detail.[3] A 51-year-old woman presented one week after a cervical epidural injection with a new occipital headache. The following day she was admitted after she developed diplopia, vertigo, nausea, and ataxia. Brain MRI was initially normal but her neurological disease progressed over the next 3 days, repeat MRI showed a small focus of diffusion restriction in the pons. Lumbar puncture was performed. The opening pressure was 34 cm H2O, while the CSF glucose was 105 mg/dl, protein 153 mg/dl, and white blood cell count 850/mm3, with 84% being neutrophils; Gram stain and culture were negative. Despite administration of acyclovir, cefepime, vancomycin, doxycycline and methylprednisolone, she continued to deteriorate and required intubation and mechanical ventilation. Repeat MRI showed areas of restricted diffusion in the pons, midbrain and cerebellum as well as diffuse meningeal enhancement. A new CSF sample was negative for several viral pathogens by PCR testing and histoplasmal and cryptococcal antigens were not detected; bacterial culture was negative. MRI of the brain showed worsening disease with brainstem infarction and ventriculomegaly, the patient continued to deteriorate and died on the 10th day, on which day Exserohilum was identified in CSF culture. Post-mortem histopathological examination of her infarcted necrotic brainstem demonstrated angioinvasive septate hyphae.

Exserohilum is a dematiaceous (dark-pigmented) filamentous fungus whose ecological niche is soil and plants. Human infections have rarely been reported with most cases involving skin and subcutaneous tissue, sinuses, and cornea, although osteomyelitis and endocarditis have been reported, as has disseminated infection in a patient with aplastic anemia.[4]

Many of the identified infections have been culture negative and only demonstrated to be due to Exoserohilum by amplification of 18S rRNA ("pan-fungal PCR") followed by sequencing. As a result, it is recommended that, in addition to fungal culture (as well as studies to rule out other causes), CSF be sent to CDC for PCR testing. Use of plant-based agar has been suggested as a means of improving recover of Exserohilum in culture. Tissue specimens should be examined histologically and samples may be preserved at -70°C for future analyses.

The amphotericin MIC of Exserohilum is reported to be 0.125-2.0 mcg/ml while that of both itraconazole and voriconazole is 0.04-0.5 mcg/ml.[5] The CDC has recommended initiation of treatment with voriconazole at 6 mg/kg every 12 hours.[6] It is further recommended that this dose, which is generally only used as a loading dose, be continued in order to increase the likelihood of achievement of adequate concentrations in the CNS. The serum concentration should be monitored with a view toward maintaining serum trough concentrations of 2-5 mcg/ml. Higher levels may be associated with an increased risk of toxicity. They also recommend consideration of the use of liposomal amphotericin B (7.5 mg/kg/d) instead in patients who present with severe disease or who fail to respond to voriconazole. CDC recommends against the intrathecal administration of amphotericin B and state "there is currently no clear evidence for the use of adjuvant steroid therapy."

CDC currently does not recommend antifungal prophylaxis for asymptomatic potentially exposed patients who received epidural injections but instead, monitoring for symptoms with consideration of performing lumbar puncture, via a site other than that at which the injection had been administered, if these occur. They do not recommend performance of lumbar puncture in asymptomatic individuals.

This is not the first outbreak of fungal infections associated with contamination of products prepared by a compounding pharmacy. John Perfect has reminded us of the lessons that should have been learned from an outbreak of 5 cases of Exophiala meningitis or arthritis related to the use of contaminated preservative-free methylprednisolone acetate prepared by a compounding pharmacy during which he was involved in the recognition and management of some of the patients.[7,8] The incubation period was reportedly as long as 6 months in one patient. The patients were treated with voriconazole with 3 of 4 with meningitis and one with sacroiliitis surviving.

An outbreak of fungal endophthalmitis involving 33 cases in 7 states occurred in March-April 2012 as the result of contamination of ocular products from a compounding pharmacy.[9] Thirteen cases were associated with use Brilliant Blue-G dye and 13 with use of triamcinolone acetate; the former infections were caused by Fusarium incarnatum-equiseti species complex and the latter by Bipolaris hawaiiensis.

As of October 19, the CDC recommends that, if not already completed, providers should contact all patients exposed to any of the three lots of MPA recalled on September 26 to inquire about symptoms. Patients who received epidural injection with medication from any of the three implicated lots of methylprednisolone acetate and who have symptoms of meningitis or posterior circulation stroke should be referred for diagnostic lumbar puncture, if not contraindicated. Patients with signs or symptoms of parameningeal infection or peripheral joint infection (e.g., increasing pain, redness, or swelling at the injection site) should be referred for diagnostic evaluation, which might include aspiration of fluid collections or joint aspiration. Although available preliminary data demonstrate incubation periods ranging from 4 to 42 days, the maximum incubation period for this infection is not known; therefore, asymptomatic but exposed patients should remain vigilant for symptoms and seek medical attention should symptoms develop. More guidance for patients and clinicians, including interim treatment guidelines, is available at http://www.cdc.gov/hai/outbreaks/meningitis.html.

A summary statement providing additional interim information for the clinician has been published. [10]

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CME Questions

1. What mechanisms or risk factors may be associated with recurrent *C. difficile* infections?

a. Relapse of the original strain via germination of residual spores.

b. Re-infection after exposure to a new strain.

c. Age 65 years or greater.

d. All of the above.

2. In the prospective study of elders with diabetes by Yau and colleagues, what HbA1c range was associated with a lower likelihood of functional decline or death?

a. HbA1c of < 7.0.

b. HbA1c of 7.0 – 7.9

c. HbA1c of 8.0 – 8.9

d. HbA1c of ≥ 9.0

3. In the study by Rognmo et al. of patients with ischemic heart disease, high-intensity exercise for cardiac rehabilitation led to what observed outcomes compared to moderate levels of exercise?

a. An increased risk of myocardial infarction with high-intensity exercise

b. A decreased risk of non-fatal cardiac arrest with high-intensity exercise

c. An increased risk of fatal cardiac arrest with high-intensity exercise

d. No significantly increased risk of adverse events

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. ■

CME Instructions

1. Read and study the activity, using the provided references for further research.

2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.*

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. Once the evaluation is received, a credit letter will be sent to you. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Beta-Blocker Use in Situations Other than Just Post-MI

Source: Bangalore S, et al. *JAMA* 2012; 308:1340-1349.

Current standard-of-care management of post-myocardial infarction (MI) patients includes long-term use of a beta-blocker, unless otherwise contraindicated. The length of the leash on this concept is not long, however, as prospective data confirming benefits of beta-blockers post-MI are limited to just a few years. Since clinicians have not been given concrete advice about when to *stop* beta-blockers, most patients are kept on beta-blockers indefinitely. Perhaps our indecisiveness is bolstered by anxieties related to the potential consequences of beta-blocker withdrawal in persons with known coronary artery disease (CAD).

In the absence of data from a randomized, prospective, long-term trial, observational data may provide some clues about the relative benefit (or lack thereof) of beta-blockers in at-risk populations. To that end, Bangalore et al report on the outcomes of three different at-risk populations from a CAD registry: post-MI patients (n = 14,043), CAD patients without history of MI (n = 12,012), and patients with CAD risk factors but no known CAD (n = 18,653). Study subjects were enrolled in 2003-2004, and followed for approximately 4 years.

Beta-blocker use was not associated with improved outcomes in *any* of the three subgroups, even the one group we take for granted that there will be beneficial effects: the post-MI group. In the 1990s, the term "cardioprotective" was sometimes used in reference to beta-blockers. Although this may be true for the few short years immediately after an MI where older clinical trials have found a benefit, whether such benefits persist, or extend to other at-risk groups, remains to be determined. ■

Long-Term Sexual and Psychological Adverse Effects of Finasteride

Source: Irwig MS. *J Clin Psychiatry* 2012;73:1220-1223.

Cutaneous dihydrotestosterone is etiologically involved in the development of male pattern baldness. Since finasteride blocks the conversion from testosterone to dihydrotestosterone, it is commonly used to treat the disorder. Systemic alpha-reductase inhibitors like finasteride are occasionally associated with sexual side effects, but only recently has there been the suggestion that finasteride-associated sexual side effects might persist beyond the time treatment is administered. Additionally, recent FDA labeling changes have added depression as a recognized adverse effect of finasteride treatment. Although mechanisms to explain persistent adverse sexual effects are unclear, some animal data suggest persistent diminution in penile relaxation and contraction subsequent to finasteride.

From a population of young men (mean age 31 years) with male pattern baldness (n = 91), Irwig compared men who reported sexual dysfunction for at least 3 months after finasteride cessation to men with male pattern baldness who had not used finasteride. Outcomes of interest were depression scores and suicidal thoughts.

Depression, depressive symptoms, and suicidal thoughts were all substantially more common in the former finasteride users than controls. For example, 75% of former users had a Beck Depression Inventory Score of at least 14 (confirming depression) as opposed to 10% of controls. It is important that clinicians recognize the potential for enduring adverse sexual and psychological symptoms associated with finasteride. ■

Novel CV Risk Markers: How Much Cluck for the Buck?

Source: The Emerging Risk Factors Collaboration. *N Engl J Med* 2012;367:14: 1310-1320.

The c-reactive protein (CRP) debate has no end in sight. While traditional risk stratification tools like the Framingham Risk Score remain well established to distinguish high- and low-risk groups, the intermediate-risk group is the population in which further refinement in risk score might be helpful. Tools like CRP and fibrinogen, when applied to persons of intermediate Framingham risk, might help identify a subgroup that merits consideration for interventions like statins.

The Emerging Risk Factors Collaboration analyzed data from prospective cohort studies (n = 246,669) that included persons free of CV disease at baseline in whom CRP, fibrinogen, and components of Framingham risk score were available. Among persons with an intermediate Framingham risk score (10-20% risk of CV event over the next 10 years), the ad-

dition of either CRP or fibrinogen to risk assessment would result in reclassification of approximately 5% from intermediate to high risk. Such risk status elevation would justify statin treatment. According to current outcomes data, statin intervention in this population would prevent one CV event for every 440 intermediate-risk persons screened. Results were similar for fibrinogen.

The results obtained are "modeled" results rather than actual outcomes. CRP and fibrinogen testing are readily available. Yet, the number needed to test for avoidance of one CV event — more than 400 — is substantial. The authors do not offer an opinion on the *propriety* of such an investigation as CRP or fibrinogen; rather, they simply provide a metric to help quantify how much cluck for the buck one might anticipate. ■

Antidepressants and Auto Accidents

Source: Orriols L, et al. *J Clin Psychiatry* 2012;73:1088-1094.

DRIVING SIMULATION TESTS PERFORMED with *healthy, non-depressed volunteers* indicate varying degrees of deleterious effect on driving skills with tricyclics (TCA) and mirtazapine, but less so with selective serotonin reuptake inhibitors (SSRIs) and venlafaxine. In direct contrast, but perhaps more pertinent to clinical medicine, trials of driving performance in *depressed patients* on antidepressants suggest better driving skills on SSRIs or mirtazapine than TCAs or venlafaxine. To gain more insight into the effects of antidepressant treatments on auto crashes, Orriols et al reviewed the database of accidents accrued by the French police force from 2005-2008 (n = 210,818).

Being on an antidepressant increased the odds ratio of being the at-fault driver by 34% compared with persons not on antidepressants. The immediate time period around initiation or change of treatment was particularly high risk. Subgroup analysis found the greatest risk among persons receiving serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine) and the least risk among TCA recipients (e.g., amitriptyline). Even though driving simulation tests suggest that depressed patients who are being treated perform better than untreated patients, clinicians must still exercise vigilance and should consider informing patients — especially upon initiation of or change in treatment — about driving risks. ■

A Different Kind of Fish Story

Source: Rizos EC, et al. *JAMA* 2012;308:1024-1033.

THE IDEA THAT OMEGA-3 POLYUNSATURATED fatty acids — a.k.a. fish oil — are beneficial stems from *some* positive randomized clinical trials. But the word "some" is limiting in the previous sentence, since some other trials do not report benefit. Rizos et al performed a systematic review and meta-analysis based on 28 studies (n = 68,680) in which adults were treated with omega-3 fatty acids for primary or secondary prevention of cardiovascular disease.

Studies were reported between 1999-2010, and averaged 2 years of follow-up, although some data went as long as 6.2 years. The majority of trials were secondary prevention trials, which — because they represent a higher risk group — might be anticipated to more readily demonstrate risk reduction.

Contrary to popular opinion, this meta-analysis was unable to confirm any positive effects of omega-3 fatty acids, whether the metric was all-cause mortality, cardiac death, sudden death, MI, or stroke. Most of the trials used combinations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), leaving open the possibility that an EPA or DHA individually might have produced different results. The authors conclude that their data support neither the routine inclusion of omega-3 fatty acids in clinical practice nor guideline recommendations that advocate their use. ■

Risk of Cancer in RA Patients Treated with Disease-Modifying Drugs

Source: Lopez-Olivo MA, et al. *JAMA* 2012;308:898-908.

IN THE EARLY YEARS OF TREATMENT EXPERIence with biologic response modifiers (BRMs) for rheumatoid arthritis (RA), concern was raised that the immune-modulating effects responsible for dramatic symptomatic improvement might also lead to increased risk for cancer. Indeed, based on excess cases of lymphoma reported in the Adverse Event Reporting System database among children and adolescents treated with BRMs, the FDA recommended a warning label for all TNF-inhibitors. Should we be worried about cancer risk in patients treated with BRMs?

Lopez-Olivo et al performed a data analysis on randomized, controlled trials (n = 63 trials) of BRM treatment in RA patients in which a BRM was compared with placebo or another traditional therapy such as methotrexate (n = 29,423). A wide variety of BRMs was included in the analysis (e.g., abatacept, adalimumab, anakinra).

This dataset was restricted to trials with at least 6 months' duration. No signal for increased risk of cancer was discerned. Although a trend for increased risk of lymphoma was found, the numbers did not achieve statistical significance. It is not possible to determine whether longer-term outcomes in relation to BRMs will be impacted by cancer risk, since this dataset is comprised of studies of 3 years' duration or less. Additionally, whether RA patients who have already suffered a cancer are at greater risk of recurrence subsequent to BRM treatment is unknown. The dramatic RA disease remission we have come to commonly see thanks to treatment with BRMs appears to be safe from an increased risk for cancer. ■

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