Delirium at the End of Life

TO THE EDITOR: For the treatment of delirium near the end of life, Casarett and Inouye (1) emphasize haloperidol, “which one randomized, controlled trial has shown to be superior to benzodiazepines” in hospitalized patients with AIDS who become delirious. This trial (2) compared haloperidol, chlorpromazine, and lorazepam with no placebo arm. A total of 6 patients received lorazepam, all had adverse effects, and the authors stopped that arm of the trial. Eleven patients received haloperidol, and 13 received chlorpromazine; there was no important difference between these two neuroleptic agents.

When biological plausibility is considered, it is not obvious that a drug that ameliorates the symptoms of a young schizophrenic person should also be expected to help a patient who develops acute, fluctuating disturbances of consciousness because of sepsis, hypotension, adverse drug reactions, brain metastases, or any of the common causes of delirium. Therefore, the rationale for using haloperidol seems weak, and as the authors note, haloperidol is toxic. Substitution of a potentially less toxic, atypical antipsychotic agent would not be evidence based and has other drawbacks. Risperidone, for example, costs about 91 times as much as generic haloperidol (3).

We also agree with Dr. Finucane about the limitations of the clinical trial cited (1). However, the recommendation supporting haloperidol was based not on this clinical trial alone but also on the consensus of palliative care clinicians as well as our own experience. Benzodiazepines are not recommended as a first-line treatment in the management of delirium near the end of life, since they are likely to produce sedation that many patients and families find unacceptable. When sedation is desirable, we prefer chlorpromazine, which produces sedation with less risk for respiratory depression. In general, however, we maintain that haloperidol offers the best balance of effectiveness and toxicity. We agree with Dr. Finucane that there is no current evidence to support the use of atypical antipsychotic agents. We also agree that treatment goals should always be set and that modification of the treatment regimen may be required to meet these goals.

With regard to the biological plausibility of the effectiveness of haloperidol for treatment of delirium, several lines of evidence have suggested that imbalance or hyperactivity in the dopaminergic system may contribute to delirium (2, 3). Thus, a dopamine-blocking agent such as haloperidol may well demonstrate beneficial effects. The benefits of haloperidol for the hallucinations, delusions, paranoia, and agitation that may accompany delirium are certainly in line with its well-documented effectiveness for similar symptoms of dementia as well as schizophrenia. Therefore, we continue to support and recommend haloperidol as first-line treatment for delirium at the end of life. We hope that future studies will be undertaken to provide a solid evidence base to guide end-of-life care.

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References

Clinical Trials Testing the Homocysteine Hypothesis

TO THE EDITOR: Bostom and colleagues (1) described the effect of mandated folic acid fortification of cereal grain products on the statistical power of several large trials assessing the effects of total homocysteine-lowering therapy for the potential reduction of cardiovascular disease outcomes. Increased exposure to folic acid–fortified flour products has affected recruitment in the Vitamin Intervention for Stroke Prevention trial, leading those investigators to decrease the total homocysteine level used as an inclusion criterion from 10.5 μmol/L to 9.5 μmol/L for men and to 8.5 μmol/L for women.

We have had similar difficulties in recruiting older adults for a clinical trial investigating the potential of vitamin B12 and folic acid supplementation to reduce the risk of stroke, myocardial infarction, and other cardiovascular events. A reduction in homocysteine levels occurred in both the placebo and intervention groups in our trial (2), consistent with findings from a recent meta-analysis (3). The effect on homocysteine levels in the intervention group was statistically significant, but we experienced difficulty recruiting a sufficient number of participants to achieve the required power for this study.

With increasing awareness of the relationship between homocysteine levels, cardiovascular disease, and vitamin therapy among both patients and clinicians, the nutrient fortification and supplementation programs have experienced increased interest, and we have had trouble recruiting older adults for our study. These findings suggest that increased homocysteine-lowering may not be a sufficient criterion for including older adults in clinical trials of this type, and other variables must be considered when recruiting and designing such trials.

Prevention of Recurrent Cardiovascular Disease
The American College of Physicians–American Society of Internal Medicine End-of-Life Care Consensus Panel was convened to synthesize the best available evidence to guide end-of-life care. It was on the basis of the best available evidence that our recommendations were formulated.

We also agree with Dr. Finucane about the limitations of the

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References

IN RESPONSE: Dr. Finucane correctly points out that few data are available to guide the management of delirium in patients near the end of life. We strongly agree that research to guide the treatment of delirium is urgently needed, and that this fact was a major area of emphasis in our article. However, in the absence of evidence from robust clinical trials, our recommendations are based on evidence provided by the medical literature, consensus of expert opinion, and our clinical experience in the care of patients at the end of life. In fact, the American College of Physicians–American Society of Internal Medicine End-of-Life Care Consensus Panel was convened to synthesize the best available evidence to guide end-of-life care. It was on the basis of the best available evidence that our recommendations were formulated.

With regard to the biological plausibility of the effectiveness of haloperidol for the treatment of delirium, several lines of evidence have suggested that imbalance or hyperactivity in the dopaminergic system may contribute to delirium (2, 3). Thus, a dopamine-blocking agent such as haloperidol may well demonstrate beneficial effects. The benefits of haloperidol for the hallucinations, delusions, paranoia, and agitation that may accompany delirium are certainly in line with its well-documented effectiveness for similar symptoms of dementia as well as schizophrenia. Therefore, we continue to support and recommend haloperidol as first-line treatment for delirium at the end of life. We hope that future studies will be undertaken to provide a solid evidence base to guide end-of-life care.

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References
study assessing the effects of low- and moderate-dose folic acid sup-
plementation on endothelial function in persons 70 years of age or
older. Homocysteine levels increase with age, and use of vitamin
supplements is common in this age group because of perceived but
untested health and cardioprotective benefits (2, 3). Literature before
the era of folic-acid flour fortification described total homocysteine
levels that averaged approximately 13 μmol/L in community-dwelling
older adults (4). However, we screened 80 community-dwelling
older men and women (mean age ± SD, 76.5 ± 4.8 years [range, 69
to 88 years]) who were not taking multivitamin or folic acid supple-
ments and found that the total homocysteine level was only
9.6 ± 2.5 μmol/L (range, 5.2 to 20.0 μmol/L); only 8 persons had
levels of 12.0 μmol/L or greater. Therefore, older adults are another
patient population exposed to folic acid–fortified cereal grain flour in
which the “homocysteine hypothesis” may not be able to be tested
adequately.

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Infliximab Therapy for Complicated sarcoidosis

TO THE EDITOR: Yee and Pochapin (1) report a case of sarcoidosis that is
desperately not only for the dramatic response to infliximab
but also for the unusual presentation. As discussed, this case repre-
sents empirical evidence of a novel therapy. The results from many
pathophysiological studies make this therapeutic response entirely
plausible. Gene polymorphisms of tumor necrosis factor-α (TNF-α)
that lead to elevated levels of circulating TNF-α have been found
in patients with sarcoidosis, and TNF-α is expressed within sarcoid
granulomas (2).

Since the report describes such an unusual presentation for a
case of sarcoidosis, it is worth reiterating that TNF-α might be the
key not only to sarcoidosis but also to granuloma formation in gen-
el. Even in the absence of lymphocytosis, TNF-α seems to be ne-
necessary and sufficient to induce granuloma formation (3). Results of
pathophysiological studies, therefore, are consistent with the impres-
sion that there is significant overlap between the protein clinical
manifestations of sarcoidosis and other granulomatous diseases. This
fact impinges heavily on the differential diagnosis, particularly when
the presentation is unusual. Although Yee and Pochapin are to be
commended for their pursuit of the diagnosis and their innovative
approach to therapy, it is surprising that they did not report the

serum immunoglobulin levels. The granulomatous variant of com-
mon variable immunodeficiency can mimic sarcoidosis in almost
evry respect, except that common variable immunodeficiency is as-
associated with IgG deficiency while sarcoidosis usually causes poly-
clonal hypergammaglobulinemia (4). Severe gastrointestinal involve-
ment, even in the absence of overt infection, is certainly more
common in common variable immunodeficiency than in sarcoidosis,
and there is a paradoxical association between common variable im-
munodeficiency and humoral autoimmunity. Finally, granulomatous
common variable immunodeficiency is also associated with elevated
levels of TNF-α and has been shown to respond to TNF-α blockade (5).

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ing patients for both active and inactive (“latent”) tuberculosis before starting treatment with infliximab, and instructing patients to seek medical advice if signs or symptoms of tuberculosis appear. We believe that physicians should be aware of the risk for reactivation of tuberculosis in persons treated with infliximab, especially those with granulomatous diseases like Crohn disease and sarcoidosis, where tuberculosis could be the real culprit.

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References

IN RESPONSE: We thank Dr. Cook and Dr. O’Connor and his colleagues for their interest in our article. Their comments underscore the diagnostic and therapeutic challenges associated with atypical presentations of granulomatous diseases. Dr. Cook insightfully points out that the granulomatous variant of common variable immunodeficiency can be confused for sarcoidosis. Although not presented in our article, immunofixation electrophoresis of our patient’s serum in fact demonstrated polyclonal hypergammaglobulinemia, and while serum IgG and IgM levels were not quantitatively assessed, serum IgA levels (determined in anticipation of possible intravenous gammaglobulin therapy for the antiphospholipid antibody syndrome) were normal. These data are thus more consistent with sarcoidosis, which is associated with hypergammaglobulinemia, and less consistent with common variable immunodeficiency, which is characterized by panhypogammaglobulinemia. Nonetheless, we firmly agree with Dr. Cook that the clinical similarities between sarcoidosis and granulomatous common variable immunodeficiency probably reflect common pathophysiologic pathways and therefore suggest potentially overlapping therapeutic approaches. Animal models and human studies implicate TNF-α in the pathogenesis of granulomas. Mice deficient in either TNF-α or TNF receptor I exhibit impaired granuloma formation in response to bacterial antigens (1, 2); as pointed out by Dr. Cook and in our report, various lines of evidence suggest that active granulomatous disease in humans is associated with increased production of TNF-α. It is therefore not surprising that certain features of granulomatous common variable immunodeficiency may respond to TNF-α inhibition (3) and that additional cases of refractory sarcoidosis responding to infliximab have been reported by Baughman and Lower (4).

Dr. O’Connor and colleagues warn of the potential exacerbation of occult Mycobacterium tuberculosis infections with anti-TNF-α therapies. We would extend this caution to include all types of infection, especially atypical ones such as other mycobacteria or fungi that may be more difficult to identify and may in fact mimic systemic inflammatory disorders. In our patient, corticosteroids and infliximab were not initiated until we were reasonably comfortable that infectious causes were excluded. Postlicensure reports of infections in the setting of infliximab and etanercept therapy have included tuberculosis, listeriosis, Pneumocystis carinii pneumonia, herpesvirus infections, and candidiasis (5). Vigilance and suspicion for active or latent infectious conditions are essential before, during, and after anti-TNF-α treatment, as they would be with any immunosuppressive therapy. Moreover, since TNF-α may contribute to tumor surveillance and immune tolerance, we further recommend that, with anticipated wider use of anti-TNF-α therapies, physicians must also maintain increased awareness of potential oncologic and autoimmune complications.

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References

Colitis Associated with Variant Clostridium difficile

TO THE EDITOR: In their report of a case of fatal pseudomembranous colitis associated with a variant Clostridium difficile strain, Johnson and colleagues (1) did an impressive job of characterizing the toxin B–producing variant and emphasizing that “clinical laboratories and clinicians who rely solely on toxin A immunosassay to diagnose C. difficile disease should recognize the possibility of C. difficile diarrhea in patients with negative test results.” The laboratory studies performed on the isolate were informative, and the telephone survey revealing that half of the hospitals in the Chicago, Illinois, area rely exclusively on the assay for toxin A provided a clear warning.

However, we believe that a simpler reminder is equally important. Subsequent to antibiotic use for an unrelated condition, the 86-year-old man discussed by Johnson and colleagues was followed...
for 2 months and had diarrhea, cramps, and sometimes fever. He had even had a positive culture for *C. difficile*. During that period, repeated tests (including computed tomography and colonoscopy that suggested pseudomembranous colitis) were performed—that is, there was an appropriately high degree of suspicion—but his illness never treated. The current fashion of withholding treatment until there is laboratory proof of a diagnosis (with the goal, in part, of not "overusing" antibiotics) is contrary to logical medicine. If this patient had been prescribed oral cholestyramine after the first stool specimen had been obtained, there would have been no interference with the investigation and his symptoms would probably have been relieved in a day. If not, oral metronidazole or vancomycin could have been added, again with minimal risk and a high probability of control. They were not given. The patient died.

We need laboratories, but clinical judgment is still the key to good medicine. As for the idea that physicians should be criticized for starting antibiotics before laboratory “proof” of their appropriateness, one might revisit the 1974 comment by Eugene A. Stead Jr.: “I believe that the early and promiscuous prescribing of antibiotics has eliminated mastoiditis and acute staphylococcal osteomyelitis. I don’t believe antibiotics given in accordance with scientific principles established by our leaders in infectious diseases would have accomplished this.”

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Reference

IN RESPONSE: We appreciate the comments by Drs. Deming and Hyman and agree that laboratory testing should not replace clinical judgment. As we pointed out in our report, there were ample clinical clues to the diagnosis of *C. difficile* colitis that were ignored in light of the laboratory test results. We also agree that empirical therapy should be initiated in a seriously ill patient if the epidemiologic and clinical features are consistent with the diagnosis. Cholestyramine, however, is not recommended as a first-line therapy for *C. difficile*-associated diarrhea. Although there are anecdotal reports of success (1), binding resins such as colestipol did not appear more effective than placebo in a comparative clinical trial (2). Furthermore, these resins may also bind antibiotics such as vancomycin (3) and should therefore not be used in combination for treatment of *C. difficile*-associated diarrhea.

It is important to perform diagnostic tests for *C. difficile* to confirm clinical diagnoses and guide the clinical management of patients, particularly because response to appropriate therapy often takes several days and relapse or recurrent infections are common (4). As highlighted by our report, it is important to recognize the limitations of diagnostic testing or, to put it another way, the “tyranny of the test results,” and use clinical judgment when laboratory test results deviate from clinical evidence. It is also important to appreciate the potential presence of variant strains of *C. difficile* to explain why toxin A test results may be unexpectedly negative. Since the publication of our report, we have been contacted by clinicians from two different states who also reported fatal cases of pseudomembranous colitis in which stool specimens were toxin A-negative and specific therapy for *C. difficile* was not initiated. Genotypic and phenotypic analyses of these strains are being conducted.

We agree that clinical judgment remains critical to optimum patient care. For practitioners, it is imperative to remember that even the best of immunologic assays for *C. difficile* toxins remain no more than 80% sensitive for laboratory confirmation of this disease (5).

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References

Effect of Angiotensin-Converting Enzyme Inhibitors on Progression of Nondiabetic Renal Disease

TO THE EDITOR: In our article on angiotensin-converting enzyme (ACE) inhibitors and progression of nondiabetic renal disease (1), we stated that regimens containing ACE inhibitors are more effective in slowing the progression of nondiabetic renal disease than regimens that do not include them. Drs. Schrier and Estacio, in their accompanying editorial (2), consider our findings “an exciting hypothesis that warrants confirmation” and state that meta-analysis cannot produce definitive conclusions. Others have concluded, however, that a well-conducted meta-analysis of randomized clinical trials of individual patient data provides the highest level of evidence in support of a therapeutic intervention (3).

All of the studies included in our meta-analysis, even the placebo-controlled studies, used concomitant antihypertensive agents to achieve a target blood pressure of less than 140/90 mm Hg. We reported the results separately for the five studies that compared ACE inhibitor groups and placebo groups, as well as for the six studies that compared ACE inhibitor groups and nonplacebo groups. The results were not substantially different from each other or from the results in the entire group. This justifies the pooling of both types of studies
Ischemic Colitis Associated with Anti-β₂ Glycoprotein-I Antibody

TO THE EDITOR: Ischemic colitis associated with the antiphospholipid syndrome has been attributed to lupus anticoagulants and antiphospholipid antibodies. Anti-β₂ glycoprotein-I antibodies appear to correlate more closely with the diagnosis of the antiphospholipid syndrome than antiphospholipid antibodies (1), and they increase the risk for deep venous thrombosis and pulmonary embolism in patients without systemic lupus erythematosus (2, 3). We report a case of ischemic colitis in a woman who used oral contraceptives and had elevated levels of anti-β₂ glycoprotein-I IgM antibodies.

A 25-year-old nonsmoking woman who had used oral contraceptives for 2 years presented with abrupt onset of severe abdominal pain and bloody diarrhea. Tenderness in the left lower quadrant of the abdomen and a midystolic murmur were noted. Colonoscopy revealed extensive superficial ulcerations with focal petechial hemorrhage in the distal descending colon, and colonic biopsy showed mucosal necrosis with edema and hemorrhage consistent with ischemic colitis. The mesenteric arteries and veins appeared normal on magnetic resonance angiography. Thrombophilic evaluation was remarkable for elevated levels of anti-β₂ glycoprotein-I IgM antibody (20.5 U [normal value <12.9 U]), whereas levels of anti-β₂ glycoprotein-I IgG, antiphospholipid antibodies (IgG and IgM) and lupus anticoagulants (dilute Russell viper venom test) were within normal limits. Levels of protein C, protein S, antithrombin III, plasminogen, and homocysteine, as well as results of tests for factor V Leiden mutation and prothrombin G20210A mutation, were unremarkable. Echocardiography with contrast revealed mild mitral regurgitation. The patient discontinued oral contraceptives, her abdominal symptoms resolved during anticoagulant therapy with warfarin, and she had no subsequent thrombotic event over the next 15 months.

Women who use oral contraceptives have a sixfold relative risk for ischemic colitis (4). Patients with anti-β₂ glycoprotein-I antibody have a 12.6-fold cumulative risk for recurrent venous thromboembolism (5). We hypothesize that elevated levels of anti-β₂ glycoprotein-I IgM antibody further increases the risk for ischemic colitis in patients using oral contraceptives. Case–control studies are indicated to determine the prevalence of anti-β₂ glycoprotein-I antibody and its value as a risk factor in evaluation of patients with ischemic colitis.

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References

CORRECTION

Correction: Angiotensin-Converting Enzyme Inhibitors and Progression of Nondiabetic Renal Disease

In an article on angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease (1), the normal mean value for urine protein excretion, given in the first full sentence on page 83, should be 0.05 g/d (50 mg/d), not 0.5 g/d.

Reference