Could Increasing the Duration of Triple Therapy Be a Clinically Useful Strategy?

TO THE EDITOR: We would like to congratulate Fuccio and colleagues (1) on their well-performed meta-analysis comparing different durations of triple therapy for *Helicobacter pylori* infection. However, we disagree with their conclusion that prolonging treatment is unlikely to be a clinically useful strategy. In our opinion, this statement is not supported by their results. The authors confirm previous findings (2, 3) that extending duration of treatment from 7 days to 10 or 14 days improves eradication rates, although the improvements in eradication rates (4% for 10 days and 5% for 14 days) were slightly lower than those previously reported (3% for 7 days, 8% for 10 days, and 12% for 14 days) (2, 3). They also found that extending treatment from 7 to 10 days increases efficacy in patients with nonulcer dyspepsia (relative risk difference, 11%) but not in patients with ulcer (relative risk difference, 2%) (4).

We disagree with the conclusion for 3 reasons. First, it is based on a subanalysis of only 4 studies with high Jadad scale scores (5) that did not find statistically significant differences. Any subanalysis limited to 4 studies is likely to give negative results because of the small sample size and the consequent type II error; it cannot be used to argue for the lack of an effect. Second, their results show that the increase in eradication rates depends on the proportion of patients with nonulcer dyspepsia included in the meta-analysis. Therefore, the inclusion of 2 large studies dealing exclusively with patients with ulcer could only have led to an underestimation of the benefit of prolonging treatment. In fact, as we currently treat more patients with nonulcer dyspepsia than patients with ulcer, the benefit of lengthening duration of treatment is likely to be greater in clinical practice than Fuccio and colleagues’ study suggests. Finally, eradication rates with triple therapy seem to be decreasing, and second- and third-line therapies often achieve suboptimal results as well. In this scenario, even a 4% to 5% increase in eradication rates is probably worth the greater cost, especially because there is no increase in side effects.

In conclusion, we believe that the correct inference from the meta-analysis is that prolonging *H. pylori* treatment statistically significantly increases eradication rates. Whether it represents a clinically useful strategy remains a matter of opinion until new evidence emerges.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We appreciate the comments of Dr. Calvet and colleagues, who disagree with our conclusion that prolonging triple therapy is unlikely to be a clinically useful strategy.

One of the aims of our meta-analysis was to verify whether current European and U.S. recommendations (1, 2) that support 14 days as the duration of choice reflect the available data. Undoubtedly, increasing the duration of treatment from 7 to 14 days will statistically significantly increase the eradication rate by 5% (95% CI, 2% to 8%); however, this improvement is substantially lower than what was previously accepted (12%) (3).

A statistically significant finding is not necessarily clinically significant in daily clinical practice. In the U.S. trial comparing different durations of triple therapy (4), 2 regimens were considered therapeutically equivalent if the CI was within the equivalence range of −15% to 15%. Of note, this cut-off was decided in consultation with the U.S. Food and Drug Administration (4). The result of our meta-analysis was largely within this range (CI, 2% to 8%).

Dr. Calvet and colleagues suggested that the inclusion of the 2 large studies of patients with peptic ulcer could have provided an underestimation of the benefit of prolonging treatment. We performed a sensitivity analysis excluding these 2 large studies, and the result did not substantially change (7% [CI, 3% to 11%]). As expected, the difference slightly increases, but the range was, again, largely within the equivalence range.

Finally, a cost-effectiveness analysis performed by Dr. Calvet and associates (5), and on the basis of a 9% increase in eradication with the longer therapy duration, concluded that “7-day therapy seems the most cost-effective strategy.”

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When to Switch Therapy in Patients with Severe Community-Acquired Pneumonia

TO THE EDITOR: We read with great interest the recent Update in Hospital Medicine by Amin and Pistoria (1). However, this summary overplayed the strength of the article by Oosterheert and colleagues (2), and we disagree with the recommendations. Oosterheert and colleagues’ article (2) was a ground-breaking, randomized, controlled trial that examined 2 strategies of conversion from intravenous to oral antimicrobial therapy in patients hospitalized with community-acquired pneumonia. Unfortunately, this article had several limitations, such as lack of a true cohort of participants with severe pneumonia—the overall 28-day mortality rate was 5% versus the generally accepted rate of 20% to 30% (3)—and exclusion of participants who required intubation or admission to an intensive care unit. In addition, this study used antibiotic regimens that, at least in the United States, would be considered inappropriate (4). Such antibiotic regimens have been associated with increased mortality compared with other antimicrobial regimens that are in line with the American Thoracic Society Infectious Diseases Society of America clinical practice guidelines (4, 5). Therefore, the recommendation by Amin and Pistoria to switch patients hospitalized with pneumonia from intravenous to oral antibiotics at 3 days is inappropriate because it is based on a single trial with major limitations. We agree with Amin and Pistoria that there is a need to switch patients from intravenous to oral therapy as soon as possible, but we recommend use of the well-validated criteria that already exist (4). Furthermore, it is important to recognize that many factors must be taken into consideration, including the patient’s condition, bacterial resistance, and antibiotic pharmacokinetics (4). Additional research and validation are needed before recommending an aggressive management strategy for severe pneumonia, which has a 30-day mortality rate approaching 30%.

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References

IN RESPONSE: We thank Dr. Mortensen and colleagues for their recent letter in regards to our Update in Hospital Medicine, which referred to the article by Oosterheert and colleagues (1). We acknowledge that the original trial by Oosterheert and colleagues has potential limitations (some of which were listed by Dr. Mortensen and colleagues), but the concept of switching from intravenous to oral therapy has been documented in the literature as a strategy for care in community-acquired pneumonia. The 2007 combined American Thoracic Society Infectious Diseases Society of America guidelines (2) for community-acquired pneumonia give a strong recommendation with level II evidence, stating that therapy should be switched from intravenous to oral when patients are hemodynamically stable, are improving clinically, are able to ingest medications, and have a normally functioning gastrointestinal tract. An early switch to oral antibiotics in patients with community-acquired pneumonia allows for early discharge and reduces drug and treatment costs. Previous studies have evaluated only mild-to-moderate disease, whereas the study by Oosterheert and colleagues was the first to look at the potential role for early-switch therapy in patients with severe community-acquired pneumonia. Such studies are needed to determine whether the early-switch strategy works in patients with more severe disease.

We appreciate that the antibiotic regimen is different from that used in the United States, but this Dutch study based its regimen choice on local Dutch guidelines. We recommend that a similar study be repeated using local U.S. guidelines in patients with severe community-acquired pneumonia. The 2007 American Thoracic Society Infectious Diseases Society of America guidelines recommend not switching antibiotics, but continuing with the regimen started and shown to be effective in the hospital, or at least staying with the same class of antibiotics. So the concept of switch therapy may be more related to maintaining the same class of antibiotics, and the question of which antibiotic to start with should be based on local guidelines.

One should not read too much into the study by Oosterheert and colleagues. It is a good randomized, controlled trial and is the first to suggest that early transition to oral antibiotics (using local guidelines for antibiotic choice) may be safely implemented in patients with severe, community-acquired pneumonia who do not need treatment in the intensive care unit. This strategy may reduce intravenous treatment and duration of hospital stay. Further studies are recommended.

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Does Tiotropium Reduce Hospitalizations in Chronic Obstructive Pulmonary Disease?

TO THE EDITOR: Because no studies have shown a clear survival benefit with any inhaled therapies for chronic obstructive pulmonary disease (COPD), the next most important hard outcome would be hospitalization rates. In their systematic review, Wilt and colleagues (1) concluded that the reductions in hospitalizations with inhaled therapies were inconsistent, and evidence did not permit definitive conclusions about relative effectiveness. I agree that that is true with long-acting β-agonists (LABAs) and inhaled corticosteroids. However, recent meta-analyses have shown that tiotropium consistently reduced hospitalization rates in moderate-to-severe COPD (2, 3). Pooled analyses, including such recent studies as TORCH (Towards a Revolution in COPD Health) (4), were conducted to update previous studies, and tiotropium is still the only inhaled therapy that consistently and significantly reduced hospitalizations (Forest plots are available at http://pulmccm.blogspot.com) (5–14). Although the TORCH study showed a statistically significant reduction in hospitalizations with combined LABA and inhaled corticosteroid therapy, not enough data are available to conduct a pooled analysis on COPD-related hospitalizations. In a recent Canadian study (15), tiotropium also reduced hospitalizations when it was combined with an inhaled corticosteroid and an LABA but not when it was combined with an LABA alone. In conclusion, currently available evidence suggests that tiotropium or a combination of inhaled corticosteroid and LABA should be the therapy of choice in stable, moderate-to-severe COPD.

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: We thank Dr. Oba for his comments, in which he concludes that tiotropium is the preferred therapy for management of chronic, stable COPD. His conclusion is based on a meta-analysis of 4 tiotropium studies demonstrating a —6% risk difference (95% CI, −10% to −2%) in the annual rate of hospitalizations compared with placebo, as well as a lack of a statistically significant reduction against placebo for studies of inhaled corticosteroids or LABAs that reported this outcome. We described similar findings in our review. The proportion of participants requiring hospitalization for COPD was lower with tiotropium than with placebo (risk difference, −2% [CI, −4% to −1%]).
We identified 42 eligible randomized, controlled trials of inhaled therapies. However, few reported hospitalizations. When reported, reductions were not consistently observed, and very few studies assessed comparative effectiveness across categories of long-acting inhalers. Of the 10 eligible tiotropium studies, only 5 reported hospitalizations and 4 used placebo controls. Only 1 of these studies demonstrated statistically significant benefit. The difference in effectiveness estimates for annual rates compared with the proportion of participants hospitalized is probably due to some participants requiring recurrent hospitalizations. The clinical significance of these pooled reductions in hospitalizations and the preferred analytic method are not known. Furthermore, investigators have demonstrated that selective study or outcome reporting (publication bias) results in biased (and more positive) effectiveness estimates (1). Therefore, we do not agree that these findings are sufficient to draw comparative effectiveness conclusions.

Data for other outcomes did not support the superiority of a particular class of long-acting inhaler. Many patients with symptomatic COPD placed an equal or greater value on obtaining a noticeable improvement in respiratory health status or reduction in exacerbations rather than a reduction in hospitalizations. No studies directly compared tiotropium with inhaled corticosteroids. Tiotropium did not provide a clinically noticeable improvement in the average respiratory health status scores versus placebo, and there were no statistical or clinical differences versus LABA. On the basis of pooled results of the 2 comparative studies, tiotropium did not reduce exacerbations compared with LABA. None of the inhaled monotherapies reduced mortality versus placebo (relative risk with tiotropium, 0.94 [CI, 0.60 to 1.47]). Combination therapy with LABA and inhaled corticosteroids reduced mortality versus LABA (relative risk with tiotropium, 0.94 [CI, 0.69 to 0.98]). The absolute reduction of 1% was not statistically significant.

On the basis of the available results, we conclude that the current level of evidence does not allow a determination of whether any long-acting inhaled therapy (or combination of these therapies) is superior to any other for management of chronic, stable COPD (2). Additional large, long-term, randomized trials comparing relative effectiveness and harms are needed.

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References

How to Improve Coordination of Care

TO THE EDITOR: The recent article by Farber and colleagues (1) and the accompanying editorial by Bodenheimer (2) highlight a rapidly growing problem: coordinating clinical care in an environment in which patient management is increasingly decentralized.

The American Geriatrics Society has expressed concern over this issue previously (3, 4) and has been working with members of the U.S. Congress to develop support for the proposed Geriatric Assessment and Chronic Care Coordination Act. A key element of this legislation is a call for the development of care plans that support coordinated care for Medicare beneficiaries with multiple chronic conditions and for reimbursement adjustments reflecting these priorities.

Addressing the need for care coordination is increasingly important not only because of the many professionals providing care in the current health care system—especially in the treatment of chronic disease—but also because of the growing need for electronic and telephone communication in clinical care. Recognition of the latter has resulted in greater emphasis on electronic medical records.

Inefficient, inadequate coordination of care not only endangers patients, it sets the stage for redundant testing and preventable complications and hospitalizations, thereby increasing health care costs (5, 6). These consequences are of particular importance in the care of the elderly: In 2002, more than one half of all Medicare beneficiaries were treated for 5 or more conditions (7). For these patients, who are especially likely to interface with multiple caregivers, out-of-office communication and support are particularly important.

It is therefore essential to make enhanced coordination of care feasible not only between physician and patient but also among caregivers. Payment reform is essential to making this a reality. The proportion of the geriatrician’s time spent in facilitating patient care outside the office visit underlines this need.

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Disclaimer: The views expressed are those of the American Geriatrics Society and not necessarily those of the U.S. Department of Veterans Affairs.

Potential Financial Conflicts of Interest: Employment: U.S. Department of Veterans Affairs Pharmacy Benefits Management. Dr. Semla serves as advisor to Evercare and on the Omnicare P&T Committee.

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TO THE EDITOR: As discussed in Farber and colleagues’ article (1) and its accompanying editorial (2), all primary care physicians would certainly enjoy getting reimbursed for the time and energy they spend on coordinating care.

But there is a serious drawback that should be considered: The “coordinating care” function may degenerate into a dumping ground for all those time-consuming tasks that are shunned by every other care provider. It would become analogous to, but much more onerous than, the scut work that first-year medical residents do. If it does, then the coordinating care function will become so burdensome that it will interfere with actually taking care of patients. Eventually, it may be the only thing that the primary care physician does. It would relegate the personal physician to a medical broker, acting as a go-between for specialists, nursing homes, home health agencies, physical therapists, and other agencies.

Most primary care physicians are already overwhelmed by the paperwork involved with those tasks that fall under the rubric of “coordinating care.” Increasing the scope of that responsibility and paying for it may give primary care physicians some satisfaction in the short term, but any promise it holds for improving their plight carries a risk for backfiring.

For instance, can you imagine the paperwork and oversight primary care physicians will be subjected to in trying to prove that they really did the coordinating work they claim to have done? Worse, there will be temptation for some to abuse this new payment code.

The best way to deal with the added work of coordinating care is to pay primary care physicians more for their services without adding a special coordinating function payment.

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Potential Financial Conflicts of Interest: None disclosed.

References


TO THE EDITOR: Budnitz and colleagues (1) recently reported on emergency department visits attributed to adverse drug reactions in the elderly. Although the authors identified medications that represent an important safety risk to the elderly, we disagree with their conclusion that the “Beers criteria medications caused low numbers of and few risks for emergency department visits for adverse events.” Their method of identifying attribution of risk may be severely flawed for several reasons.

The authors required that the emergency department physician explicitly attribute the diagnosis to use of medication. Most emergency department physicians would not miss the fact that hypoglycemia or hyperglycemia was related to insulin use or the fact that bleeding with an elevated international normalized ratio was related to warfarin use. Elevated digoxin levels are easily measured as well. However, these physicians would probably be far less likely to recognize that an antihistamine contributed to a fall-related injury, delirium, or urinary retention. Indeed, they might not even have known that the patient was using the drug. Without a chart review, the investigators may have significantly underestimated the contribution of drugs listed in the Beers criteria. We are surprised that this limitation was not even discussed.

We are also perplexed that the authors seem to have ignored the other 5.3% of emergency department visits listed in Table 3 of their article that were caused by medications in the Beers criteria (digoxin, short-acting benzodiazepines, nonsteroidal anti-inflammatory drugs, and others). Table 3 also shows that 3 of the 4 most commonly implicated medications (warfarin, aspirin, and clopidogrel) accounted for 27.7% of the emergency department visits. The authors chose not to use the part of the Beers criteria that identifies additional medications as potentially inappropriate if prescribed to patients who have certain preexisting conditions (2). However, this section of the Beers criteria lists aspirin as inappropriate in patients with gastric ulcers. Both aspirin and clopidogrel are listed as inappropriate for older adults receiving anticoagulant therapy. Without knowing the patients’ medications and comorbid conditions, the authors could not determine whether drugs in the Beers criteria were involved in many of the cases. We believe that the conclusions of this study are flawed because of poor study design.

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IN RESPONSE: We thank Dr. Golden and colleagues for their response to our recent article. They brought up several interesting issues, but we believe the critical issue for patient safety is identified by Dr. Krishnamurthy in his online letter (1). The estimated 59 000 emergency department visits each year caused by adverse events from the use of insulin, warfarin, and digoxin are harms that should be addressed. We stand by our conclusions that performance measures and interventions targeting the use of warfarin, insulin, and digoxin could prevent more emergency department visits for adverse events than measures targeting the use of “potentially inappropriate” medications.

Dr. Golden and colleagues suggest that by relying on the diagnoses of emergency department physicians, we probably did not identify some adverse events—such as falls for which a sedating antihistamine might have been a contributing factor—that may have been identified if we had performed complete chart reviews. We indeed acknowledged the limitations that adverse events “diagnosed and treated in other settings (for example, in primary care offices, in urgent care centers, or during hospitalizations) or not treated in any health care facility were not included” and that our surveillance methods were “probably less sensitive than [those of] research studies involving chart review” (2). The data we presented were not based on epidemiologic associations, but rather on counts of physician diagnoses and treatments rendered. Exhaustively reviewing charts to identify antihistamine use in a patient who has fallen and then designating the antihistamine as a contributing factor post hoc is problematic. In fact, a recent review of prescribing for the elderly (3) concluded that the evidence that potentially inappropriate prescribing is associated with adverse patient outcomes is “mixed and contradictory.”

Performance measures and interventions to improve medication safety for older patients are important. These measures should be based on scientific soundness, feasibility, and relevance, particularly the ability to improve measurable patient outcomes (4). The estimated 5.3% of emergency department visits attributed to medications that are potentially inappropriate in certain circumstances and the fraction of emergency department visits from antiplatelet agents among patients with gastric ulcers or concomitant anticoagulation represent important subsets of patients. The Beers criteria provide useful guidance for optimizing medication use in elderly adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163:2716-24. [PMID: 14662625]

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References

Are Pay-for-Performance Programs a Threat to Medical Professionalism?

TO THE EDITOR: It was gratifying to read Snyder and Neubauer’s position paper (1) on pay-for-performance and to see that I am not alone in my concerns over these initiatives. I would like to comment on a few issues.

First, health care providers are the only certain beneficiaries of pay-for-performance. Therefore, the implementation of pay-for-performance programs, without evidence of patient benefit, is inconsistent with the ethical imperative that “[c]linicians must ensure that . . . a medically appropriate level of care takes precedence over personal consideration” (1). In that regard, pay-for-performance seems inherently unethical.

Second, the goal of reducing substandard care is an acknowledgment of widespread failure by the medical profession to meet the “professional duty to provide high-quality care to each patient” while accepting payment for it. Rather than addressing substandard care with a coordinated action plan (which could include limitations on scope of practice and possible disciplinary action), pay-for-performance places the considerations of the medical profession ahead of those of the patients by offering more money to underachieving providers to do what they should have been doing all along—and what their on-par colleagues have been doing all along without financial inducement. Are patients not entitled to quality care that meets professional standards on the initial payment, just as we are all entitled to goods and services that meet industry standards in any other business transaction? Extra money should not be necessary for service providers to meet their own industry standards.

Third, by failing to recognize the difference between physicians who performed the minimum years of postgraduate training required for licensure and those who completed residency and fellowship training, pay-for-performance devalues internal medicine and its subspecialities. It condenses years of training into a brief list of performance parameters and perpetuates the myth that all physicians possess the same knowledge and skill sets.

Finally, is there any doubt that the increased profitability of the diseases included in the performance parameters will parallel an increase in reported frequency? I offer 2 examples of what I have seen...
in the peer-review process. Among overweight patients with normal fasting blood sugar, in the absence of pharmacotherapy a diagnosis of “diabetes” modified by “diet-controlled” has been used to justify extensive and repetitive laboratory testing—not just glucose and hemoglobin A1c, but also chemistry panels, complete blood cell count, and fructosamine levels. Among patients with no convincing evidence of hypertension, a diagnosis of “hypertension” modified by “diet-controlled” has been used to justify repetitive electrocardiography, echocardiography, stress testing, renal perfusion scans, and other tests. Because pay-for-performance lacks diagnostic and exclusionary criteria, word games of this nature will proliferate and, in the absence of oversight, remain hidden. The inaccurately reported data will increasingly contaminate public health and other demographic records used by government and private industry to determine budgetary allocations.

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Potential Financial Conflicts of Interest: None disclosed.

Reference

TO THE EDITOR: The paper by Snyder and Neubauer (1) about pay-for-performance and medical ethics falls short. Recently, I had 2 patients—a husband and wife who were both overweight and had diabetes—become angry with me when I discussed the need to diet. I held my tongue and did not turn them away.

When Germany developed the first antibiotic sulfa drugs in the 1930s, only the United States allowed their use without adequate research. Multiple patients died from dangerous unregulated formulations, and this led to the formation of the U.S. Food and Drug Administration. Don’t we have a responsibility to our patients to test any new system to determine whether it is valid? Shouldn’t pay-for-performance be tried with a test population to see whether the concept really works?

This program will especially affect the physicians and patients in small practices that do not have the resources to put pay-for-performance into practice. Large clinics and their satellites can hire extra clerical staff and at least not lose money. But what about the rest of us? Although Snyder and Neubauer say that it would be unethical for physicians to drop more difficult patients, it definitely will happen. There have been several attempts of litigation against managed care companies for restriction of care, but these companies have been safeguarded by unethical government protection. Internists who can will retire earlier, creating an ugly situation of untried legislation. When government gets between patients and their physician, everybody loses.

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Reference

TO THE EDITOR: Snyder and Neubauer (1) correctly depict pay-for-performance as a possible threat to professionalism in medicine. The contradiction between professionalism and pay-for-performance is, however, more serious than the authors acknowledge.

The core concept of professionalism is the physician’s willingness to put self-interest aside and to address the interests of the patient as the first priority (2). However, pay-for-performance is predicated on the idea that we can get physicians to serve patients well only by appealing to their self-interest. The models are radically contradictory.

Are all financial incentives designed to improve physician behavior—in ways that would better serve patients—therefore an unacceptable challenge to professionalism? That seems too radical a conclusion. Professionalism requires that the patient–physician relationship never be reduced to a purely mercantile encounter; yet many aspects of medical practice can be improved by the use of good business methods. The line between financial incentives that support and those that undermine professional behavior may be a fine one, as illustrated by debates over the ethics of the relationship between medicine and the pharmaceutical industry (3). Pay-for-performance proposals can navigate these risks only if they are subjected to considerably more ethical scrutiny than they have received to date.

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References

IN RESPONSE: We appreciate Dr. Metoyer’s thoughtful comments, many of which the American College of Physicians Ethics, Professionalism, and Human Rights Committee agree with in the College’s pay-for-performance position paper. We do not agree, however, with her conclusion that, in some regards, pay-for-performance programs are inherently unethical. Every payment system creates incentives and potential conflicts of interest, such as the incentives in fee-for-service payment to increase care or the incentives under capitation to do less rather than more. The College believes pay-for-performance programs have promise if they can be focused on patient perspectives on care and professionalism, including the duty to ensure medically appropriate care before financial and other considerations. As pointed out in the ACP Ethics Manual (1), “medical practice” does not stand still. Clinicians must be prepared to deal with changes and reaffirm what is most important. The pay-for-performance ethics paper attempts to lay out principles that may guide clinicians in...
dealing with pay-for-performance programs, as well as provide ethical
guidance to those who would design such systems. The problem
of current payment systems rewarding substandard care and then
paying again to improve that care goes beyond pay-for-performance
programs.

Dr. Lowther suggests that pay-for-performance is an untested
strategy to improve quality of care and that the concept should be
tested before being instituted in widespread fashion. We noted the
lack of evidence of effectiveness in our paper. Nongovernmental pay-
ers are looking at that now in our market-based system, and ques-
tions have begun to appear regarding the effectiveness of pay-for-
performance strategies in this setting (2). Dr. Lowther also implies
that pay-for-performance is primarily a government function, but
that is not currently the case. In fact, the Physician Quality Report-
ing Initiative program instituted by the Centers for Medicare &
Medicaid Services thus far is not a pay-for-performance program but
rather a pay-for-reporting program with modest monetary incentives.
Nonetheless, we do agree that the risk for deselection of patients is
serious and caution that this risk may increase if pay-for-performance
programs grow in the current payment environment.

Dr. Brody raises the specter that pay-for-performance may
threaten medical professionalism even more than depicted in our
paper. The College’s hope is to redirect the evolution of incentives
for quality by insisting on a focus that puts the needs of the patient
first. Fundamental reform of the payment system to encourage com-
prehensive, coordinated care of the patient would achieve much
more than widespread deployment of pay-for-performance. If that
were to happen, pay-for-performance programs could play a small
but significant role in encouraging certain outcomes, as long as pro-
fessionalism principles and safeguards against unwanted outcomes
were built in.

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[PMID: 18293832]

CLINICAL OBSERVATIONS

Memantine-Induced Hepatitis with Cholestasis in a Very Elderly Patient

Background: Memantine, recently approved in Europe and the
United States for treating dementia, has been shown to reduce clinical deterioration in moderate-to-severe Alzheimer disease and in vas-
cular dementia (1). To our knowledge, there are no reports of hepato-
toxicity during treatment with memantine.

Objective: To describe a case of memantine-induced hepatotox-
icity in a very elderly patient with mixed, moderate dementia and behavior disorders.

Case Report: A 92-year-old white woman with hypertension and
heart failure (New York Heart Association class II to III) had mixed,
moderate dementia and behavior disorders. She was on a home care
program and was taking digoxin, 0.125 mg/d; lisinopril, 5 mg/d;
tiapride, 50 mg/d; alprazolam, 0.25 mg/d; and promazine, 10 mg/d.
The patient recently began treatment with memantine, 5 mg/d for
the first 8 days and 10 mg/d for the next 8 days. On day 16, the
patient suddenly developed jaundice associated with dark urine and
itching. The patient did not have fever, nausea, vomiting, or abdom-
inal pain. Murphy sign was negative; there was no evidence of hep-
tosplenomegaly or ascites. The Table shows the results of routine
laboratory tests performed 24 hours after the onset of signs and
symptoms and during follow-up. At day 1, serologic tests showed
increased levels of aspartate aminotransferase (AST), alanine amino-
transferase (ALT), γ-glutamyltransferase, total and direct bilirubin,
and alkaline phosphatase (ALP). Memantine treatment was immedi-
ately discontinued. The patient continued her other medications,
and the signs and symptoms of hepatitis improved. Laboratory tests
5 days later showed a partial recovery in levels of AST, ALT, and
total and direct bilirubin, whereas levels of γ-glutamyltransferase
and ALP remained elevated. The levels of serum IgA, IgG, IgM, C3, and
C4 were normal. The patient was negative for hepatitis A, B, and C
virus antibodies and antimitochondrial antibodies and had a negative
direct Coombs test result. Ultrasonography of the liver, spleen, and
pancreas excluded mechanical obstruction. Seven days after meman-
tine therapy withdrawal, the signs and symptoms had completely
disappeared. Levels of AST, ALT, γ-glutamyltransferase, total and
direct bilirubin, and ALP returned to normal after 20 days. On the
basis of biochemical, clinical, and instrumental parameters; criteria
of drug-induced liver disorders (2); and the Naranjo adverse drug reac-
tion probability scale (3), we diagnosed probable cholestatic hepatitis
induced by memantine.

Discussion: Drug-induced liver injury is a potential complication
of many medications because the liver is central to the metabolic
disposition of most drugs. Although we cannot identify a mechanism
whereby memantine causes cholestasis liver injury, memantine is
known to accumulate in lysosomes and cause phospholipidosis in
macrophages (4). This effect can induce cell vacuolization and hepa-
tocyte injury. Moreover, such drugs as memantine, which affect
transport proteins at the canalicular membrane, can interrupt bile
flow and cause cholestasis associated with a mild degree of cell
injury (5). In this patient, the time between drug intake (including
the dose increase) and the onset of signs and symptoms of hepatitis
was suggestive of drug-related toxicity. Similarly, the decrease in liver
enzyme levels in less than 8 days after treatment withdrawal suggests
a link between the use of memantine and liver injury. Finally, alter-
native causes of hepatitis were excluded, including mechanical ob-
struction of the main bile or intrahepatic ducts, viral hepatitis, and
primary biliary cirrhosis.

Conclusion: Memantine is a probable cause of drug-induced
hepatitis with cholestasis.

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Potential Financial Conflicts of Interest: None disclosed.

References
1. Ethics and Human Rights Committee, American College of Physicians. Ethics
2. Rosenthal MB, Landon BE, Normand SL, Frank RG, Ahmad TS, Epstein AM.
[PMID: 18293832]

CLINICAL OBSERVATIONS

Memantine-Induced Hepatitis with Cholestasis in a Very Elderly Patient

Background: Memantine, recently approved in Europe and the
United States for treating dementia, has been shown to reduce clinical deterioration in moderate-to-severe Alzheimer disease and in vas-
cular dementia (1). To our knowledge, there are no reports of hepato-
toxicity during treatment with memantine.

Objective: To describe a case of memantine-induced hepatotox-
icity in a very elderly patient with mixed, moderate dementia and behavior disorders.

Case Report: A 92-year-old white woman with hypertension and
heart failure (New York Heart Association class II to III) had mixed,
moderate dementia and behavior disorders. She was on a home care
program and was taking digoxin, 0.125 mg/d; lisinopril, 5 mg/d;
tiapride, 50 mg/d; alprazolam, 0.25 mg/d; and promazine, 10 mg/d.
The patient recently began treatment with memantine, 5 mg/d for
the first 8 days and 10 mg/d for the next 8 days. On day 16, the
patient suddenly developed jaundice associated with dark urine and
itching. The patient did not have fever, nausea, vomiting, or abdom-
inal pain. Murphy sign was negative; there was no evidence of hep-
tosplenomegaly or ascites. The Table shows the results of routine
laboratory tests performed 24 hours after the onset of signs and
symptoms and during follow-up. At day 1, serologic tests showed
increased levels of aspartate aminotransferase (AST), alanine amino-
transferase (ALT), γ-glutamyltransferase, total and direct bilirubin,
and alkaline phosphatase (ALP). Memantine treatment was immedi-
ately discontinued. The patient continued her other medications,
and the signs and symptoms of hepatitis improved. Laboratory tests
5 days later showed a partial recovery in levels of AST, ALT, and
total and direct bilirubin, whereas levels of γ-glutamyltransferase
and ALP remained elevated. The levels of serum IgA, IgG, IgM, C3, and
C4 were normal. The patient was negative for hepatitis A, B, and C
virus antibodies and antimitochondrial antibodies and had a negative
direct Coombs test result. Ultrasonography of the liver, spleen, and
pancreas excluded mechanical obstruction. Seven days after meman-
tine therapy withdrawal, the signs and symptoms had completely
disappeared. Levels of AST, ALT, γ-glutamyltransferase, total and
direct bilirubin, and ALP returned to normal after 20 days. On the
basis of biochemical, clinical, and instrumental parameters; criteria
of drug-induced liver disorders (2); and the Naranjo adverse drug reac-
tion probability scale (3), we diagnosed probable cholestatic hepatitis
induced by memantine.

Discussion: Drug-induced liver injury is a potential complication
of many medications because the liver is central to the metabolic
disposition of most drugs. Although we cannot identify a mechanism
whereby memantine causes cholestasis liver injury, memantine is
known to accumulate in lysosomes and cause phospholipidosis in
macrophages (4). This effect can induce cell vacuolization and hepa-
tocyte injury. Moreover, such drugs as memantine, which affect
transport proteins at the canalicular membrane, can interrupt bile
flow and cause cholestasis associated with a mild degree of cell
injury (5). In this patient, the time between drug intake (including
the dose increase) and the onset of signs and symptoms of hepatitis
was suggestive of drug-related toxicity. Similarly, the decrease in liver
enzyme levels in less than 8 days after treatment withdrawal suggests
a link between the use of memantine and liver injury. Finally, alter-
native causes of hepatitis were excluded, including mechanical ob-
struction of the main bile or intrahepatic ducts, viral hepatitis, and
primary biliary cirrhosis.

Conclusion: Memantine is a probable cause of drug-induced
hepatitis with cholestasis.

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Potential Financial Conflicts of Interest: None disclosed.

References
1. Ethics and Human Rights Committee, American College of Physicians. Ethics
2. Rosenthal MB, Landon BE, Normand SL, Frank RG, Ahmad TS, Epstein AM.
[PMID: 18293832]
### Letters

**Table. Results of Laboratory Tests at Onset and Follow-up Days 1, 5, and 20***

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Normal Range</th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST, U/L</td>
<td>5–30</td>
<td>74</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>5–56</td>
<td>132</td>
<td>71</td>
<td>50</td>
</tr>
<tr>
<td>γ-GT, U/L</td>
<td>4–20</td>
<td>155</td>
<td>213</td>
<td>15</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>μmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.3–1.9</td>
<td>4.3</td>
<td>1.81</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>2–14</td>
<td>28.7</td>
<td>12.1</td>
<td>11.3</td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>μmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0–0.3</td>
<td>2.5</td>
<td>0.75</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>0–4</td>
<td>333.3</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>ALP, U/L</td>
<td>38–126</td>
<td>912</td>
<td>1013</td>
<td>110</td>
</tr>
<tr>
<td>Leukocyte count, $\times 10^9$ cells/L</td>
<td>4.3–10.8</td>
<td>10.3</td>
<td>7.8</td>
<td>–</td>
</tr>
<tr>
<td>IgA, mg/L</td>
<td>800–3500</td>
<td>–</td>
<td>3030</td>
<td>–</td>
</tr>
<tr>
<td>IgG, g/L</td>
<td>6.2–14.0</td>
<td>–</td>
<td>9.23</td>
<td>–</td>
</tr>
<tr>
<td>IgM, mg/L</td>
<td>450–2500</td>
<td>–</td>
<td>2230</td>
<td>–</td>
</tr>
<tr>
<td>C3, g/L</td>
<td>0.90–1.80</td>
<td>–</td>
<td>1.73</td>
<td>–</td>
</tr>
<tr>
<td>C4, g/L</td>
<td>0.10–0.40</td>
<td>–</td>
<td>0.26</td>
<td>–</td>
</tr>
<tr>
<td>Direct Coombs test</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>Anti-HAV</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>Anti-HBV</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>–</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
</tr>
<tr>
<td>Anti-AMA</td>
<td>&lt;1/20</td>
<td>–</td>
<td>Negative</td>
<td>–</td>
</tr>
</tbody>
</table>

* ALP = alkaline phosphatase; ALT = alanine aminotransferase; anti-AMA = antimitochondrial antibodies; anti-HAV = hepatitis A virus antibody; anti-HBV = hepatitis B virus antibody; anti-HCV = hepatitis C virus antibody; AST = aspartate aminotransferase; γ-GT = γ-glutamyltransferase.

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**References**


**Successful Treatment of Fulminant* Clostridium difficile**  
**Infection with Fecal Bacteriotherapy**

*Background:* A subset of patients with Clostridium difficile-associated diarrhea will develop fulminant, life-threatening C. difficile infection that is refractory to medical therapy. Surgical options for fulminant disease are associated with high mortality rates. We describe a patient with fulminant C. difficile infection successfully treated with donor stool by retention enema.

*Objective:* To describe a successful case of using fecal bacteriotherapy to treat life-threatening, fulminant C. difficile enterocolitis.

*Case Report:* A 69-year-old man was admitted to the hospital after undergoing radical prostatectomy. The patient was given perioperative, intravenous cefazolin. On postoperative day 2, the patient developed an ileus and oliguric renal failure. Two days later, the patient developed a temperature of 101 °F and began receiving piperacillin–tazobactam treatment for hospital-acquired pneumonia. Three days after starting the treatment, the patient developed hypotension; worsening abdominal distention, and foul-smelling, watery diarrhea. The patient was subsequently transferred to the intensive care unit, given intravenous metronidazole, the patient required maximum doses of 2 vasopressor agents, phenylephrine and norepinephrine throughout the patient’s sigmoid colon. Despite treatment with rectal vancomycin and intravenous metronidazole, the patient required maximum doses of 2 vasopressor agents, phenylephrine and norepinephrine by postoperative day 25, to maintain his blood pressure. The patient’s clinical picture was consistent with fulminant C. difficile infection.

After the patient agreed to proceed, the donor stool, contributed by the patient’s daughter (weight, about 45 g), was diluted with approximately 300 mL of normal saline with a 60-mL syringe and administered as a retention enema. Over the next 36 hours, the patient’s blood pressure stabilized, the leukocyte count normalized, and oliguria resolved (Figure) and both vasopressors and continuous venovenous hemofiltration was discontinued. The patient’s bowel function returned, and abdominal distention decreased. For the first time in 28 days, the patient’s diet was advanced.

*Discussion:* Fulminant C. difficile is becoming a more frequent
cause of death and complications in hospitalized patients. In a major hospital in Pennsylvania, the incidence of patients with fulminant *C. difficile* increased from 0% in 1990 to 3.2% in 2000 (1). The current standard treatment for patients with fulminant *C. difficile* who do not respond to metronidazole and vancomycin is surgical colectomy. However, recent studies show that surgical treatment of fulminant *C. difficile* colitis has a mortality rate ranging from 35% to 57% (1, 2). In one case series, the factor associated with death after colectomy was hypotension requiring preoperative vasopressors (1). This would have made our patient a poor surgical candidate.

Fecal bacteriotherapy, the transfer of stool from one person to another, has been used in various case series and reports in stable clinic patients with chronic diarrhea secondary to recurrent *C. difficile* infection. In one case series (3), 18 patients with chronic, relapsing *C. difficile* infection were administered donor stool via a nasogastric tube. In this series, the authors noted an 89% success rate without any adverse effects with receipt of donor stool. Of interest, most patients responded within 12 to 24 hours after the administration of donor stool. Other routes of administration, including colonoscopy and retention enemas, have been successful (4, 5).

**Conclusion:** Because of the increased incidence of fulminant disease and the high mortality rate associated with surgical options, it is important to find alternative ways to treat patients with fulminant *C. difficile* infection. This case demonstrates the therapeutic potential of fecal bacteriotherapy for patients with fulminant *C. difficile* enterocolitis who respond poorly to traditional metronidazole and vancomycin treatments.

**References**


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**Disclaimer:** The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the U.S. Department of the Navy, U.S. Department of Defense, or the U.S. government.

**Potential Financial Conflicts of Interest:** None disclosed.

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**Overanticoagulation with Coumarin and Cutaneous Azole Therapy**

**Background:** Overanticoagulation is a major concern in elderly patients receiving coumarin therapy. Potentiation of coumarin anti-coagulants by systemic azole antifungal agents is well documented.

![Figure. Patient’s response to stool transplantation.](http://www.annals.org/)

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**Potential Financial Conflicts of Interest:** None disclosed.
However, few data are available about coumarin interactions with topical azole agents (1–3).

**Objective:** To describe 6 cases of overanticoagulation with coumarin therapy in patients treated with topical azole.

**Methods:** Over 25 months in an 800-bed geriatric teaching hospital, all patients older than 80 years of age with an international normalized ratio (INR) greater than 5.0 who were receiving coumarin were screened for cutaneous azole use. We defined day 0 as the first day with INR greater than 5.0. For each patient, we collected demographic, clinical, and therapeutic data (especially on use of con-
comitant medications that might potentiate coumarin) at least 15 days before and after day 0 (4). We determined whether the patients had the cytochrome P4502C9 (CYP2C9) variant allele. We assessed and rated the causal relationship between cutaneous azole therapy and coumarin potentiation and the severity of potentiation, according to the criteria of Holbrook and colleagues (4).

Results: Among 123 patients treated with coumarin who had at least one INR value greater than 5.0, 6 received cutaneous azole therapy (Figure). Four of the 6 (66.7%) had an INR greater than 9.0, whereas 6 of 117 receiving coumarin without azole therapy had an INR greater than 9.0 (66.7% vs. 5.1%; odds ratio, 37 [95% CI, 5.6 to 244]; P < 0.001). No bleeding complications occurred in any of the 6 patients. Coumarin was withdrawn and vitamin K was administered in all cases. Three patients were heterozygous for a CYP2C9 variant allele, all with INR values greater than 11.0 (highest INR >20.0).

In the first patient, econazole lotion was applied to the vulva under a disposable diaper. The patient was taking ofloxacin and amoxicillin–clavulanate (started 21 days before day 0). She died of pneumonitis on day 3. The second patient had active giant-cell arteritis. Bifonazole cream was applied to her buttocks. Zolpidem and omeprazole treatments were started 4 days and 14 days, respectively, before day 0. In the third patient, econazole powder and lotion were applied to the vulva and groin under a disposable diaper. Pristinamycin, furosemide, and omeprazole therapies were started 6 days before day 0. In the fourth patient, econazole cream was applied on the groin and trunk. In the fifth patient, econazole cream was applied to the vulva under a disposable diaper. Oral clotrimoxazole treatment was started 12 days before day 0 and was withdrawn 6 days later, and fusidic acid cream was applied 14 days before day 0. Finally, the sixth patient had econazole lotion applied to the groin.

Causality was probable in 2 patients treated with econazole and possible in the 4 other patients treated with econazole or bifonazole. Concomitant medications or acute disease may have caused overanticoagulation in these 4 patients. However, cutaneous azole therapy still may have enhanced coumarin potentiation.

Discussion: We observed probable or possible potentiation of anticoagulation in older patients receiving coumarin and topical azole therapy. Of interest, we observed that econazole or bifonazole was consistently applied to large areas in all cases, and was applied under disposable diapers in half of cases. Similar observations were made in 2 recent case reports (2, 3). Cutaneous application of azole to large areas increases the risk for systemic absorption, thereby leading to marked systemic effects, especially when applied under occlusive diapers. Carrying a CYP2C9 variant allele may also have contributed to the dramatic increase in INR in 3 cases.

Conclusion: Physicians should be aware that topical econazole and bifonazole applied to large areas can dramatically increase INR values in elderly patients receiving coumarin therapy. Close INR monitoring should be recommended as long as azole therapy is used.

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Potential Financial Conflicts of Interest: None disclosed.

References

Corrections

Correction: Improved Diagnostic Evaluation of Suspected Tuberculosis

In a recent article on improved diagnostic evaluation of suspected tuberculosis (1), the Potential Financial Conflicts of Interests section contained an error. Dr. Dosanjh does not have stock ownership or options in Oxford Immunotec Ltd. This section should have read as follows: “Stock ownership or options (other than mutual funds): A. Lalvani (Oxford Immunotec Ltd), University of Oxford (Oxford Immunotec Ltd).” The 18 March 2008 audio summary (available at www.annals.org) also discusses the corrected material.

Reference

Correction: Achieving a High-Performance Health Care System with Universal Access

The American College of Physicians recently published a position paper on improving health care (1). Under Recommendation 3 on page 69, Canada was erroneously included with Australia, France, Germany, Japan, and Switzerland as countries where students pay little or no medical school tuition. The Canadian Medical Association (2) reports that the average tuition in Canada is now $12,000 and that annual tuition ranges from $2181 to $16,862.

References