

Correspondence



Resistant Bacteria in Retail Meats and Antimicrobial Use in Animals

To the Editor: Changes in policy on the use of antimicrobials must be based on a broad perspective reflecting microbial epidemiology, ecology, and resistance. The three reports on specific areas of the overall problem of antimicrobial resistance in the October 18 issue¹⁻³ are valuable, but the authors reach beyond the scope of their results in the conclusions they draw. Gorbach's editorial⁴ includes conclusions and assertions that are unsupported by his citations.

A ban on the use of antimicrobials in livestock feed could have unintended consequences and undesirable net effects on the environment, economy, and public health. Such a ban could result in increased morbidity and mortality in livestock, jeopardizing food and byproducts. There could also be a substantial increase in animal manure. The potential negative consequences to public health and the environment go far beyond the potential negative effects on livestock profitability. There are now science-based guidelines and stringent regulations for the judicious use of antimicrobials in food-producing animals.^{5,6}

It is unknown whether banning antimicrobials in livestock feed would reduce the incidence of resistant infections in humans. Premature closure of this important debate now by imposition of a ban would lead us to overlook other approaches that could be more beneficial and less costly to society. It is imperative that we use solid science and examine the expected ramifications when proposing changes in antimicrobial-use policy.

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1. White DG, Zhao S, Sudler R, et al. The isolation of antibiotic-resistant salmonella from retail ground meats. *N Engl J Med* 2001;345:1147-54.
2. McDonald LC, Rossiter S, Mackinson C, et al. Quinupristin-dalfopristin-resistant *Enterococcus faecium* on chicken and in human stool specimens. *N Engl J Med* 2001;345:1155-60.
3. Sorensen TL, Blom M, Monnet DL, Frimodt-Moller N, Poulsen RL, Espersen F. Transient intestinal carriage after ingestion of antibiotic-resistant *Enterococcus faecium* from chicken and pork. *N Engl J Med* 2001;345:1161-6.
4. Gorbach SL. Antimicrobial use in animal feed — time to stop. *N Engl J Med* 2001;345:1202-3.
5. Center for Veterinary Medicine. Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA). Rockville, Md.: Food and Drug Administration, 2002. (Accessed February 13, 2002, at <http://www.fda.gov/cvm/index/amducca/amducatoc.htm>.)
6. Center for Veterinary Medicine. CVM and judicious use of antimicrobials. Rockville, Md.: Food and Drug Administration. (Accessed February 13, 2002, at <http://www.fda.gov/cvm/fsi/juduse.htm>.)

To the Editor: In his editorial, Gorbach states that restrictions on the use of antimicrobials in food animals would provide health-related benefits. This proposal overlooks the fact that resistance in the human population is widespread because of human use of antimicrobials and will not be changed by eliminating certain veterinary uses of antimicrobials.¹

Consistently, improvements have been made in swine housing, "flow"-through production stages, the quality and nutritional value of feed, sanitation, and preventive-medicine practices. Guidelines for the judicious use of antimicrobials² are being implemented with the support of the American Association of Swine Veterinarians. All these measures have improved the health of swine and thus are essential for ensuring the safety of pork supplied to consumers.

Abolishing the use of additive antimicrobials in feed would force substantial changes in infrastructure and swine management, causing productivity losses that would cost farmers up to \$1 billion over 10 years.³ Such losses would drive family farms out of business, despite substantial gaps in the data that are needed to give confidence that there would be any real effect on antimicrobial resistance, let alone public health.

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1. Curtiss R. The benefits of antimicrobial use in agriculture: a contrarian's long view. *ASM News* 2001;67:199.
2. Judicious therapeutic use of antimicrobials. Schaumburg, Ill.: American Veterinary Medical Association, 2002. (Accessed February 13, 2002, at <http://www.avma.org/scienact/jtua/default.asp>.)
3. Hayes DJ, Jensen HH, Backstrom L, Fabiosa J. Economic impact of

INSTRUCTIONS FOR LETTERS TO THE EDITOR

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a ban on the use of over-the-counter antibiotics. Ames, Iowa: Center for Agricultural and Rural Development, Iowa State University, December 1999. (Accessed February 13, 2002, at <http://www.card.iastate.edu/publications/texts/99sr90.pdf>.)

To the Editor: White et al. report that 16 percent of 45 isolates from ground meats were resistant to ceftriaxone. This is a much higher proportion than that found by the National Antimicrobial Resistance Monitoring System (NARMS) in 1999 (0.4 percent of 1499 human-origin isolates, 0.1 percent of 1610 beef isolates, 0 percent of 1438 chicken isolates, and 0.4 percent of 470 dairy-cattle isolates, 0 percent of 876 swine isolates, and 0.8 percent of 713 turkey isolates).^{1,2} This inconsistency, combined with the substantial difference in identified serotypes between the samples studied by White et al. and those of the U.S. Department of Agriculture (USDA),^{3,4} indicates that the authors' sampling may have been confounded by contamination with salmonella that did not originate in food animals. The authors mention the potential for contamination during handling and processing. Seventeen of the 45 isolates were serotypes not found in the USDA sampling of food animals.³

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2. National Antimicrobial Resistance Monitoring System (NARMS). Washington, D.C.: Food and Drug Administration, 2001. (Accessed February 13, 2002, at <http://www.ars-grin.gov/ars/SoAtlantic/Athens/arru/narms.html>.)
3. Sarwari AR, Magder LS, Levine P, et al. Serotype distribution of salmonella isolates from food animals after slaughter differs from that of isolates found in humans. *J Infect Dis* 2001;183:1295-9.
4. James W. Salmonella serotypes from carcasses and raw ground products. In: Proceedings of the 104th Annual Meeting of the United States Animal Health Association. Richmond, Va.: Animal Health Association, 2000:504-7.

To the Editor: Although eliminating the use of antimicrobials given to promote the growth of food animals and fowl would obviously be desirable, this suggestion results in strong opposition from groups that regard any such limitations as financially harmful. A more practical way to achieve the same end would be routine irradiation of meat, poultry, and fish. Although there is much prejudice against irradiation, I believe that such prejudice would be easier to deal with than opposition to the elimination of antimicrobials because the problem is ignorance, rather than financial self-interest. Irradiation would also get rid of pathogenic *Escherichia coli*. In the present era, when much supermarket meat is prepackaged at the slaughterhouse, this approach would be very effective.

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The authors reply:

To the Editor: Barber et al. state that in our study of antimicrobial-resistant salmonella from retail ground meats, we "reach beyond the scope" of our results in drawing a con-

clusion about banning antimicrobial use in livestock feed. In fact, we did not suggest such a ban. The study demonstrated that antimicrobial-resistant salmonella are common in retail meats. The findings provide support for the adoption of guidelines for the prudent use of antimicrobials in food animals and for a reduction of pathogens in our food supply.

In response to Vogel's statement that our sampling was possibly confounded by contamination with salmonella that did not originate in food animals: we agree that it is reasonable to explore other possible sources of salmonella contamination in retail meats. However, it has been established during many years of epidemiologic investigation of outbreaks of foodborne illness that animal products are the primary source of the salmonella that cause such illness.¹ In addition, it has been shown that antimicrobial resistance in salmonella is most likely the result of antimicrobial use in food-producing animals and that most infections with antimicrobial-resistant salmonella are acquired by the consumption of contaminated food-animal products.^{2,3}

Of particular importance in our study was the recovery of five isolates of *Salmonella enterica* serotype agona that were resistant to nine antimicrobials, including ceftriaxone and ceftiofur. They were recovered from turkey or beef purchased from a single store over a two-week period. These meats had been ground at three facilities, suggesting that the source of this serotype was the meat itself. We acknowledge that some of the serotypes we recovered have not been routinely found in the USDA sampling of food animals. However, there are more than 2000 serotypes of salmonella. Serotypes identified in one study do not necessarily match serotypes identified in other studies, unless the number of salmonella isolates reaches thousands. In fact, 62 percent of our isolates belonged to serotypes routinely recovered from animals. Among the 13 serotypes we detected, 3 were among the 8 salmonella serotypes most frequently identified in animal and human isolates submitted to the NARMS surveillance system in 1998.⁴

Vogel points out that the proportion of ceftriaxone resistance we observed in isolates from meat (16 percent) is much higher than the proportion of resistant isolates reported by NARMS. However, one would not expect the NARMS data to predict the rate of contamination of retail meats. Ground retail meats are produced by the comminution of tissues from multiple carcasses and would be expected to contain salmonella at a higher rate than the NARMS samples. In addition, antimicrobial resistance in salmonella is closely associated with serotype. *S. enterica* serotype typhimurium, for example, has been found to be more resistant than other serotypes. What is important about our observations is the finding in retail meats of many serotypes with multidrug-resistant phenotypes, including ceftriaxone resistance. Therefore, we need to focus efforts on reducing the prevalence of pathogens throughout food production and processing.

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2. Seyfarth AM, Wegener HC, Frimodt-Møller N. Antimicrobial resistance in *Salmonella enterica* subsp. *enterica* serovar typhimurium from humans and production animals. *J Antimicrob Chemother* 1997;40:67-75.
3. Glynn MK, Bopp C, Dewitt W, Dabney P, Mokhtar M, Angulo FJ. Emergence of multidrug-resistant *Salmonella enterica* serotype typhimurium DT104 infections in the United States. *N Engl J Med* 1998;338:1333-8.
4. NARMS annual reports. Atlanta: Centers for Disease Control and Prevention, 2001. (Accessed February 13, 2002, at <http://www.cdc.gov/narms/annuals.htm>.)

To the Editor: Barber et al. contend that we reach “beyond the scope” of our results in the conclusions we draw. Meanwhile, the argument they make — that a ban on antimicrobials in livestock feed “could have unintended consequences and undesirable net effects on the environment, economy, and public health” — is wholly unsubstantiated. Poultry producers in Denmark, for example, voluntarily discontinued the use of all antimicrobials for growth promotion in food-producing animals, without significant untoward effects.¹ We found that nearly 60 percent of retail chickens purchased in four states were contaminated with quinupristin-dalfopristin-resistant *Enterococcus faecium* and that this resistance was probably the result of antimicrobials used in animal feed. Although we found very little evidence to date of resistance among strains isolated from humans, we stand by our conclusion that antimicrobial use in animals is a matter of concern because of possible resistance in humans in the future.

Gorbach, in his editorial, went a step further and called for closer scrutiny of all antimicrobial use in food-producing animals and an outright ban on subtherapeutic use for growth promotion. The basis for both Gorbach’s conclusions and ours is a large number of reports from various settings suggesting that antimicrobials used in food-producing animals frequently result in the transmission of clinically significant resistance to humans. Independent, prestigious scientific committees^{2,3} have examined these data and have arrived at conclusions similar to Gorbach’s. The only question that remains is how long it will take for us to act on the data already available to us.

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2. The use of antibiotics in food-producing animals: antibiotic-resistant bacteria in animals and humans: report of the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR). Canberra, Australia: Commonwealth Department of Health and Aged Care, Commonwealth Department of Agriculture, Fisheries and Forestry, 1999. (Accessed February 13, 2002, at <http://www.health.gov.au/pubs/jetacar.htm>.)
3. WHO global principles for the containment of antimicrobial resistance in animals intended for food. Geneva: World Health Organization, 2000. (Also available at http://www.who.int/emc/diseases/zoo/who_global_principles.html.)

To the Editor: A total ban on the use of antimicrobials in livestock feed has not been proposed, as argued by Bar-

ber et al., but there should be a ban on the use of antimicrobials for growth promotion as well as immediate termination of the widespread overuse of prophylactic antimicrobials in cases in which disease can be prevented by alternative strategies. Consequently, the argument concerning “increased morbidity and mortality in livestock” is not relevant.

A scientific study in Denmark found that terminating the use of antimicrobials for growth promotion in broiler chickens had no negative consequences on the animals’ health or producers’ profitability.¹ Similar experiences have been reported in fattening pigs (weight range, 30 to 100 kg). In weaned piglets, however, problems with diarrhea have been observed in some herds after discontinuation of the use of growth-promoting antimicrobials. Such problems have been managed by veterinary interventions and improved feeding and weaning procedures.

Despite recent increases in the use of therapeutic antimicrobials in swine, the total volume of antimicrobials used in animal husbandry in Denmark has been reduced by more than 60 percent (from 206 to 81 tons) with the voluntary discontinuation of the use of antimicrobials for growth promotion.² The resulting dramatic reduction in the frequency with which resistant bacteria are isolated from food animals, food, and humans has been well documented.²⁻⁵ Hence, there is sufficient scientific evidence to support urgent action. Finally, we do not share the concern expressed by Barber et al. regarding the “premature closure of this important debate.” The stamina of the animal-health industry lobby certainly precludes that.

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2. DANMAP 2000 — consumption of antimicrobial agents and resistance to antimicrobial agents in bacteria from food animals, food and humans in Denmark: report from Statens Serum Institut, Danish Veterinary and Food Administration, Danish Medicines Agency and Danish Veterinary Laboratory, 2001. (Available at <http://www.vetinst.dk/dk/Publikationer/Danmap/Danmap%202000.pdf>.)
3. Aarestrup FM, Seyfarth AM, Emborg HD, Pedersen K, Hendriksen RS, Bager F. Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. *Antimicrob Agents Chemother* 2001;45:2054-9.
4. van Den Bogaard AE, Bruinsma N, Stobberingh EE. The effect of banning avoparcin on VRE carriage in the Netherlands. *J Antimicrob Chemother* 2000;46:146-7.
5. Klare I, Badstubner D, Konstabel C, Bohme G, Claus H, Witte W. Decreased incidence of VanA-type vancomycin-resistant enterococci isolated from poultry meat and from fecal samples of humans in the community after discontinuation of avoparcin usage in animal husbandry. *Microb Drug Resist* 1999;5:45-52.

Transfusion in Elderly Patients with Myocardial Infarction

To the Editor: Wu et al. report on the benefits of blood transfusion in elderly patients with acute myocardial in-

fraction and anemia (Oct. 25 issue).¹ Their data show that among patients with hematocrit values higher than 36.0 percent, those who received blood transfusions had a higher risk of death within 30 days than those who did not receive transfusions. The authors suggest that among older patients with acute myocardial infarction and anemia, transfusions benefit those with hematocrit values of 30.0 percent or lower. A corollary is that transfusion should be avoided in those with hematocrit values above 30.0 percent who do not have active bleeding, since in such patients, transfusion is associated with a significant increase in mortality. Transfusion of red cells in patients with hematocrit values exceeding 36.0 percent may not contribute much to oxygen-carrying capacity and may actually have negative effects on perfusion and oxygen delivery in the microvasculature because of alterations in red-cell membranes in stored blood and increased viscosity caused by the transfusion of red cells.

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To the Editor: Wu et al. conclude that transfusions may improve the outcome in patients with acute myocardial infarction. In their retrospective study, the analysis was not controlled for normovolemia. The data in Table 1 of their report suggest that hypovolemia (a lower blood pressure and a higher heart rate on admission) influenced the outcome in the groups of patients with more severe anemia. Transfusions may have replaced needed volume when the administration of fluids would have sufficed. Controlling for normovolemia, Hébert et al.¹ found that a restrictive transfusion policy (target hemoglobin level, 7 to 9 g per deciliter) did not worsen mortality or morbidity in patients in the intensive care unit, including those with ischemic heart disease, whereas a liberal transfusion policy (target hemoglobin level, 10 to 12 g per deciliter) worsened morbidity (as determined by changes in scores for multiple organ dysfunction).

Did significant differences in coexisting conditions result in a bias against transfusion in the group of patients with the most severe anemia (hematocrit, 5.0 to 24.0 percent), resulting in a statistically worse outcome in this group? Table 2 of the article shows that 28.7 percent of the patients in this group received no transfusions; 33.2 percent died in the hospital. On the basis of data in Table 2, we performed a simple analysis of the correlation between blood transfusion and mortality at 30 days and found a strong positive association ($r=0.87$, $P=0.04$). Table 3 of the article shows that the two groups of patients with hematocrit values that exceeded 36.0 percent had a higher mortality rate at 30 days if they underwent transfusion than if they did not (odds ratio, 1.43 and 1.66). This negative association was attributed to "other events," rather than to transfusion. Prospective studies² have shown that higher hematocrit values after coronary-artery bypass grafting are

associated with worse outcomes (myocardial infarction and death).

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 2. Spiess BD, Ley C, Body SC, et al. Hematocrit value on intensive care unit entry influences the frequency of Q-wave myocardial infarction after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 1998;116:460-7.

To the Editor: In their editorial on anemia, transfusion, and mortality,¹ Drs. Goodnough and Bach conclude, "On the basis of the evidence presented by Wu et al., we recommend that hematocrit levels should be maintained above 33 percent in patients who present with acute myocardial infarction." This conclusion is incorrect, inasmuch as it extends the interesting, albeit debatable, findings of Wu et al. to patients under the age of 65, a population that was not included in their data review.

I agree with Goodnough and Bach that clinical evidence to support transfusion guidelines is insufficient. Very few randomized studies have been published in this area of medicine, and most recommendations are guided by consensus rather than by science. Now that we have a study (even if it remains open to discussion) on the benefits of transfusions in elderly patients with acute myocardial infarction, we must resist the temptation to extend the authors' conclusions improperly. On the contrary, we now have to conduct similar (or better) studies in all the other populations of patients who are likely to benefit from erythrocyte transfusions.

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The authors reply:

To the Editor: Albert interprets our data as suggesting that "transfusion should be avoided in those with hematocrit values above 30.0 percent . . . since in such patients, transfusion is associated with a significant increase in mortality." This statement is incorrect. We found that transfusions were associated with a reduction in 30-day mortality among patients with hematocrit levels of up to 33.0 percent in our main analysis and in six of seven subgroup analyses; transfusion had a neutral effect on survival only when patients who died within 2 days after admission were excluded from the analysis. Thus, our data suggest that there may be a benefit (and there is certainly no harm) in providing transfusions to elderly patients with myocardial infarction and hematocrit levels up to 33.0 percent. In addition, we found that transfusion had a neutral effect on 30-day mortality among patients with hematocrit levels of

33.1 to 36.0 percent. Transfusion was associated with an increased risk of death within 30 days only among patients with hematocrit levels that exceeded 36.0 percent, not among those with values exceeding 30.0 percent, as Albert contends. We are uncertain about the mechanism of this increased risk of death. Although Albert notes possible decrements in perfusion and oxygen delivery due to the transfusion of red cells, the infrequent use of transfusion in this cohort (1.9 percent of patients with hematocrit levels exceeding 36.0 percent received transfusions) leads us to suspect the influence of unmeasured events that occurred later in the hospital stay.

Perelman and colleagues suggest that the benefit of transfusion in our cohort is due to volume replacement. Furthermore, they interpret data reported by Hébert and colleagues¹ as suggesting that transfusion does not improve outcomes when used restrictively in patients in the intensive care unit who have cardiovascular disease. Although the restoration of volume in elderly patients with anemia may be of benefit, our multivariable analysis accounted for the possible effects of hypovolemia by adjusting for the mean arterial pressure and heart rate. This analysis suggests a survival benefit in addition to the restoration of volume, possibly by means of an improvement in the delivery of oxygen through stenosed coronary arteries or ischemic tissue because of elevated hemoglobin levels.²

In addition, Perelman and colleagues misrepresent the data reported by Hébert et al. They reported a consistent trend toward higher mortality rates (4.0 percent or higher) up to 60 days after admission among patients with ischemic heart disease who were treated according to the restrictive transfusion strategy. Their findings were not statistically significant because the analysis (with a total of 257 patients) had power to detect only a 17.0 percent absolute difference in mortality rates. Recognizing this trend, Hébert et al. reported that a restrictive transfusion strategy appears to be safe in critically ill patients with cardiovascular disease, "with the possible exception of patients with acute myocardial infarcts and unstable angina."¹

Randomized, controlled trials are needed to determine definitively the appropriate transfusion thresholds for elderly patients hospitalized with anemia and myocardial infarction. In the absence of these data, well-designed and carefully analyzed observational studies can provide important insights into the clinical care of this population of patients.

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2. Hébert PC, Hu LQ, Biro GP. Review of physiologic mechanisms in response to anemia. *CMAJ* 1997;156:Suppl 11:S27-S40.

The editorialists reply:

To the Editor: Dr. Hardy raises an important issue regarding the generalizability of our recommendation — based on the report by Wu et al.¹ of findings in Medicare patients 65 years of age or older — to maintain hematocrit levels above 33 percent in patients hospitalized with myocardial infarction. Since the mean age of patients admitted to hospitals in the United States in 1999 with a primary diagnosis of myocardial infarction was 68 years,² the results are relevant to the majority of patients, although a substantial minority may be younger than 65 years of age. We commented in our editorial that "the generalizability of the findings to younger patients . . . remains an open question." But in the absence of any data to the contrary, the question is really whether we can assume that a more conservative approach to transfusion will result in optimal outcomes for younger patients or others with myocardial infarction whose demographic characteristics do not match those of the population included in the Cooperative Cardiovascular Project.

We believe that, in aggregate, the data support the hypothesis that a more liberal threshold for blood transfusion benefits patients with myocardial infarction regardless of their age group. Two large observational studies noted an association between a hemoglobin level below 9.5 to 10.0 g per deciliter and increased mortality among patients with cardiovascular disease and suggested that such patients do not tolerate anemia as well as patients with other conditions.^{3,4} Hébert et al.⁴ observed that when the hemoglobin level was less than 9.5 g per deciliter, red-cell transfusion led to a 40 percent decrease in mortality among severely ill patients with cardiovascular disease. In addition, in a recent prospective, randomized trial, within the subgroup of patients who also had ischemic heart disease, patients assigned to a restrictive approach to transfusion (with a target hemoglobin level of 7 to 9 g per deciliter) had a 30-day mortality rate that was 5 percent higher than that among patients assigned to a liberal approach to transfusion (with a target hemoglobin level of 10 to 12 g per deciliter) ($P=0.38$).⁵

Obviously, the risk of death for patients with myocardial infarction involves additional factors that are independent of age. Younger patients with large and complicated infarctions may also have limited reserve and heightened vulnerability to anemia. We believe it to be most prudent not to assume that anemia and transfusions affect the outcomes in patients with myocardial infarction differently depending solely on whether they are 65 or more years of age or are younger. Furthermore, we believe it is consistent with the best evidence that is currently available to recommend maintaining the hematocrit at 33 percent or higher in patients admitted to the hospital with acute myocardial infarction, regardless of their age.

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2. Rogers WJ, Canto JG, Lambrew CT, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the U.S. from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2, and 3. *J Am Coll Cardiol* 2000;36:2056-63.
3. Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996;348:1055-60.
4. Hébert PC, Wells G, Tweeddale M, et al. Does transfusion practice affect mortality in critically ill patients? *Am J Respir Crit Care Med* 1997;155:1618-23.
5. Hébert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001;29:227-34.

Infective Endocarditis

To the Editor: Mylonakis and Calderwood (Nov. 1 issue)¹ cite the increasing use of transesophageal echocardiography in determining the duration of antibiotic therapy for *Staphylococcus aureus* bacteremia.² Proponents of this approach contend that clinical assessment alone is inadequate to distinguish patients with endocarditis from those with uncomplicated bacteremia.²⁻⁴ However, this new paradigm conflicts with much of the earlier literature.⁵

Transesophageal echocardiography has operationally redefined endocarditis. But does the diagnosis of staphylococcal endocarditis always mandate at least four weeks of treatment with antibiotics? *S. aureus* endocarditis identifiable exclusively by transesophageal echocardiography may be routinely cured with shorter courses of antibiotics, as with β -lactam monotherapy for tricuspid endocarditis in the absence of evidence of left-sided involvement.⁶ Although subclinical endocarditis often complicates seemingly uncomplicated *S. aureus* bacteremia, an extended course of antibiotics is not necessarily indicated.⁴⁻⁶ Reflexive use of transesophageal echocardiography may be superfluous at best and injurious at worst in the management of short-lived, clinically uncomplicated, catheter-associated *S. aureus* bacteremia in patients with native valves.

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2. Fowler VG Jr, Li J, Corey GR, et al. Role of echocardiography in evaluation of patients with *Staphylococcus aureus* bacteremia: experience in 103 patients. *J Am Coll Cardiol* 1997;30:1072-8.
3. Fowler VG Jr, Sanders LL, Sexton DJ, et al. Outcome of *Staphylococcus aureus* bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. *Clin Infect Dis* 1998;27:478-86.
4. Fowler VG Jr, Sanders LL, Kong LK, et al. Infective endocarditis due to *Staphylococcus aureus*: 59 prospectively identified cases with follow-up. *Clin Infect Dis* 1999;28:106-14.
5. Raad II, Sabbagh MF. Optimal duration of therapy of catheter-related *Staphylococcus aureus* bacteremia: a study of 55 cases and review. *Clin Infect Dis* 1992;14:75-82.
6. Ribera E, Gomez-Jimenez J, Cortes E, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis: a randomized, controlled trial. *Ann Intern Med* 1996;125:969-74.

To the Editor: As Mylonakis and Calderwood point out, renal disease associated with bacterial endocarditis in-

cludes infarcts, abscesses, and glomerulonephritis, ranging from focal glomerulonephritis to diffuse glomerulonephritis that is sufficient to cause the impairment of renal function.^{1,2} However, in rare cases, rapidly progressive glomerulonephritis develops.^{1,2} Antibiotics are usually recommended as the first treatment of choice,^{1,2} although some cases do not respond to antibiotic therapy and progress to end-stage renal failure and then to renal death, resulting in the need for dialysis therapy.

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1. Neugarten J, Gallo GR, Baldwin DS. Glomerulonephritis in bacterial endocarditis. *Am J Kidney Dis* 1984;3:371-9.
2. Weinstein L, Schlesinger JJ. Pathoanatomic, pathophysiologic and clinical correlations in endocarditis. *N Engl J Med* 1974;291:1122-6.

To the Editor: I found the review of endocarditis by Mylonakis and Calderwood informative and helpful. However, I am concerned about one detail.

Wilson et al.¹ established guidelines for the treatment of endocarditis caused by viridans streptococci. The category of "penicillin-susceptible viridans streptococci" is defined by a minimal inhibitory concentration (MIC) of 0.1 μg per milliliter or less. The category of "relatively penicillin-resistant streptococci" includes a group for which the MIC of penicillin is more than 0.1 to 0.5 μg per milliliter and another group for which the MIC is more than 0.5 μg per milliliter. These guidelines are presented in the review by Mylonakis and Calderwood, as well as in others.^{2,3}

To my knowledge, penicillin-susceptible streptococci of the viridans group have always been defined by a MIC of 0.12 μg per milliliter or less, not 0.1. This point may seem inconsequential, but according to the guidelines, when the MIC for an organism is 0.12 mg per milliliter, since it is more than 0.1, it should be treated as a relatively resistant organism. I disagree and have assumed instead that the guidelines in the original article, and in every one that has followed (including the *Sanford Guide to Antimicrobial Therapy*³), are based on an error, as a result of a well-meaning editor having rounded the value down to the nearest one decimal place.

In addition, since the only MIC value that is more than 0.12 and less than 0.5 μg per milliliter is 0.25, I have assumed that the only streptococci to be treated with a two-week course of gentamicin are those with an MIC of exactly 0.25 μg per milliliter.

Finally, since resistant viridans streptococci (MIC, $>4 \mu\text{g}$ per milliliter) have been identified, it would be helpful to define viridans streptococci with intermediate susceptibility as organisms for which the MIC is 0.25 to 4.0 μg per milliliter, rather than more than 0.1, 0.12, or 0.5 μg per milliliter.

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1. Wilson WR, Karchmer AW, Dajani AS, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. *JAMA* 1995;274:1706-13.
2. Bayer AS, Bolger AF, Taubert KA, et al. Diagnosis and management of infective endocarditis and its complications. *Circulation* 1998;98:2936-48.
3. Gilbert DN, Moellering RC, Sande MA. The Sanford guide to antimicrobial therapy. 31st ed. Hyde Park, Vt.: Antimicrobial Therapy, 2001.

The authors reply:

To the Editor: Dr. DiNubile agrees that in some patients subclinical endocarditis may follow uncomplicated *S. aureus* bacteremia but raises the question of whether an extended course of antibiotics in such patients is always necessary. Transesophageal echocardiography allows the detection of vegetations and the diagnosis of definite endocarditis, according to the Duke criteria, in approximately 25 percent of patients with catheter-associated *S. aureus* bacteremia, and these patients have a higher mortality than patients with *S. aureus* bacteremia who do not have endocarditis.¹ Although patients in whom vegetations are detected only by transesophageal echocardiography (and not by transthoracic echocardiography) have a better outcome than patients in whom vegetations are detected by transthoracic echocardiography,² we are not aware of convincing, controlled data suggesting that left-sided, catheter-associated *S. aureus* endocarditis is as effectively treated with a two-week course of antibiotics as it is with a four-week course. Therefore, we believe that transesophageal echocardiography is a useful adjunct in decision making with regard to the duration of antibiotic therapy in patients with catheter-associated *S. aureus* bacteremia; transesophageal echocardiography has also been shown to be a cost-effective strategy in such patients.^{3,4}

We appreciate the comments of Koya et al. on the rare cases of endocarditis in which rapidly progressive glomerulonephritis develops in association with the infection. Space constraints prevented us from mentioning all potential renal complications of this protean illness in our article.

Dr. Baxter comments that the breakpoints for susceptibility to penicillin that are used to determine the treatment of streptococcal endocarditis according to the American Heart Association's guidelines⁵ differ from the breakpoints for susceptibility used in the clinical microbiology laboratory to report a streptococcal isolate as "susceptible," "intermediate," or "resistant." The American Heart Association's guidelines suggest treating streptococci with an MIC of penicillin that is less than or equal to 0.1 μg per milliliter as susceptible; this category includes streptococci with an MIC of penicillin that is 0.06 μg per milliliter or less. On the basis of these guidelines, strains with an MIC of 0.12 or 0.25 μg per milliliter are treated as relatively resistant, and those with an MIC greater than or equal to 0.5 μg per milliliter are treated in the same way as enterococci.

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1. Fowler VG Jr, Li J, Corey GR, et al. Role of echocardiography in evaluation of patients with *Staphylococcus aureus* bacteremia: experience in 103 patients. *J Am Coll Cardiol* 1997;30:1072-8.

2. Fowler VG Jr, Sanders LL, Kong LK, et al. Infective endocarditis due to *Staphylococcus aureus*: 59 prospectively identified cases with follow-up. *Clin Infect Dis* 1999;28:106-14.
3. Rosen AB, Fowler VG Jr, Corey GR, et al. Cost-effectiveness of transesophageal echocardiography to determine the duration of therapy for intravascular catheter-associated *Staphylococcus aureus* bacteremia. *Ann Intern Med* 1999;130:810-20.
4. Heidenreich PA, Masoudi FA, Maini B, et al. Echocardiography in patients with suspected endocarditis: a cost-effectiveness analysis. *Am J Med* 1999;107:198-208.
5. Wilson WR, Karchmer AW, Dajani AS, et al. Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. *JAMA* 1995;274:1706-13.

Hypochondriasis

To the Editor: Dr. Barsky's Clinical Practice review of hypochondriasis (Nov. 8 issue)¹ omits a common and important feature of the symptom complex in many patients: anxiety-induced hyperventilation. The symptoms mentioned in the review — intermittent paresthesias, belching, atypical chest pain, chronic headache, dizziness, and tinnitus — are the typical manifestations of hyperventilation.² Unfortunately, most physicians ascribe these symptoms to organic causes and subject patients to multiple, unnecessary, and often expensive diagnostic studies. Even more unfortunately, these studies have false positive rates as high as 30 percent, as has been demonstrated with regard to exercise stress tests in women with atypical chest pain.³ The vicious cycle often leads to multiple, unnecessary, and frequently expensive therapies.

Fortunately, if anxiety-induced hyperventilation is considered and the symptom complex can be reproduced by voluntary overbreathing, the syndrome can be recognized easily. Even more fortunately, relief can be provided once the patient understands the mechanism responsible for his or her symptoms. Prevention and immediate relief of symptoms may be attained by rebreathing into a paper sack, and longer-term relief may be attained through cognitive behavioral therapy that includes the use of controlled breathing exercises.⁴

Some patients may need one of the 10 drugs listed in Barsky's Table 2 for further relief. But rather than rushing into pharmacotherapy, practitioners should consider a process, hyperventilation, that is probably involved in the symptoms of many psychosomatic syndromes. Conditions associated with hyperventilation certainly include chronic fatigue, fibromyalgia, and panic attacks, and very likely also include the Gulf War syndrome and chronic Lyme disease, in addition to other common psychosomatic conditions.⁵ Various factors may be responsible for the initial anxiety, but hyperventilation marks a common path from anxiety to disabling symptoms.

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1. Barsky AJ. The patient with hypochondriasis. *N Engl J Med* 2001;345:1395-9.
2. Kaplan NM. Anxiety-induced hyperventilation: a common cause of symptoms in patients with hypertension. *Arch Intern Med* 1997;157:945-8.

3. Fleet RP, Dupuis G, Marchand A, Burelle D, Arsenault A, Beitman BD. Panic disorder in emergency department chest pain patients: prevalence, comorbidity, suicidal ideation, and physician recognition. *Am J Med* 1996; 101:371-80.
4. Barlow DH, Gorman JM, Shear MK, Woods SW. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA* 2000;283:2529-36. [Erratum, *JAMA* 2000;284: 2450, 2597.]
5. Wessely S, Nimmuan C, Sharpe M. Functional somatic syndromes: one or many? *Lancet* 1999;354:936-9.

Dr. Barsky replies:

To the Editor: Anxiety-induced hyperventilation is a prominent feature of panic attacks and panic disorder, and the prevalence of diagnosable panic disorder is high among patients with hypochondriasis.^{1,2} The prominence of cardiorespiratory symptoms in panic disorder may make this condition particularly difficult to distinguish from acute cardiac or pulmonary disease. Dr. Kaplan is correct in pointing out that once panic anxiety has been diagnosed, several effective therapeutic approaches are available, of which pharmacotherapy is only one. If the patient is having infrequent, uncomplicated panic attacks with limited symptoms, I agree that behavioral techniques, such as rebreathing and relaxation training, are both indicated and effective. If the panic attacks are more frequent and involve other symptoms and if the patient meets the diagnostic criteria for panic disorder, cognitive behavioral therapy is an effective alternative to pharmacotherapy.

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1. Barsky AJ, Wyshak G, Klerman GL. Psychiatric comorbidity in DSM-III-R hypochondriasis. *Arch Gen Psychiatry* 1992;49:101-8.
2. Noyes R Jr, Kathol RG, Fisher MM, Phillips BM, Suelzer MT, Woodman CL. Psychiatric comorbidity among patients with hypochondriasis. *Gen Hosp Psychiatry* 1994;16:78-87.

Case 27-2001: Waldenström's Macroglobulinemia

To the Editor: In Case Record 27-2001 (Aug. 30 issue),¹ Table 1 and the discussion by Dr. Noopur Raje contain errors. Neither multiple myeloma nor the classic (or pure) form of Waldenström's macroglobulinemia is marked by massive splenomegaly. Massive splenomegaly is rarely a feature of Hodgkin's disease.

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1. Case Records of the Massachusetts General Hospital (Case 27-2001). *N Engl J Med* 2001;345:682-7.

The discussant replies:

To the Editor: I agree that Table 1 is somewhat misleading. It should have been entitled "Hematologic Diseases

Associated with Splenomegaly and Anemia." The causes of massive splenomegaly mentioned in the discussion include chronic myeloid leukemia, agnogenic myeloid metaplasia, and polycythemia vera. Variants of certain other hematologic cancers, such as chronic lymphocytic leukemia of the prolymphocytic type, and lymphoproliferative disorders, such as marginal-zone lymphoma, are other causes. Although splenomegaly has been described in multiple myeloma, Hodgkin's disease, and Waldenström's macroglobulinemia, these diseases certainly do not constitute the common causes of massive splenomegaly.

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Aortic Pseudocoarctation Causing Refractory Hypertension

To the Editor: We report a case of pseudocoarctation of the aorta caused by an intraluminal calcific mass. A 49-year-old woman who smoked and had had hypertension for eight years was evaluated for an intramural aortic hematoma seen on magnetic resonance imaging (MRI). She had recently been examined because of uncontrollable hypertension and transient acute renal dysfunction. Magnetic resonance angiography and captopril-augmented renal scanning excluded the presence of renal-artery stenosis, a renal biopsy excluded the presence of parenchymal disease, and tests of urine and plasma excluded the presence of pheochromocytoma, Cushing's syndrome, and Conn's syndrome. The patient also had intermittent claudication. She presented to the referring hospital with low back pain and severe hypertension (220/100 mm Hg). MRI suggested the presence of an intramural hematoma at the thoracic level.

Transferred for further evaluation, she had a brachial blood pressure of 230/70 mm Hg; occasionally, her blood pressure was 305/135 mm Hg. She had weak femoral pulses and a continuous murmur in the interscapular region. Her blood pressure was controlled with esmolol and nitroprusside. Transesophageal echocardiography revealed a complex, calcified, and fixed mass limited to the lumen of the descending aorta that was approximately 10 cm in length; it began as a shelf-like projection and became more complex, with ridges and furrows and areas of severe luminal narrowing (90 percent of the cross-sectional area). Doppler ultrasonography revealed a gradient of 145 mm Hg. There were prominent paraaortic collateral vessels that fed back into the aorta distal to the mass, consistent with a chronic obstruction. A computed tomographic scan confirmed that the mass was overtly calcific and solely intraluminal. This was confirmed at surgery by the normal appearance of the external aortic wall (Fig. 1). Surgical excision with interposition of a tube graft was performed.

Microscopical examination showed no evidence of an intimal tear or adventitial disease. The mass had the appearance of a calcific organized thrombus. On gross inspection and histologic examination, there were no atherosclerotic



Figure 1. Gross Pathological Specimen of the Excised Portion of the Descending Thoracic Aorta, Showing the Smooth External Aortic Wall and the Complex Intraluminal Mass.

changes in the specimen, no evidence of neoplasia, and no sign of any major intimal damage that might have caused the lesion. An evaluation for thrombophilia revealed that the patient was heterozygous for the common prothrombin mutation. She had had a postpartum deep venous thrombosis years earlier.

The constellation of signs and symptoms correlated entirely with the location of and physiological disturbances associated with the lesion — the syndrome of aortic pseudocoarctation. The amenability of the lesion to surgery, the complete correction of the hypertension, and the unsuspected thrombophilia were striking aspects of the case.

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