Correspondence

Routine Use of Antibiotics in Food Animals Increases Protein Production and Reduces Prices

SIR—In the policy context of assessing whether developing countries that want cheaper, more-plentiful meat would be well-advised to use animal antibiotics, Collignon and colleagues reported in a recent article that "Some persons argue that the routine addition of antibiotics to animal feed will help alleviate protein undernutrition in developing countries by increasing meat production. In contrast, we estimate that, if all routine antibiotic use in animal feed were ceased, there would be negligible effects in these countries. Poultry and pork production are unlikely to decrease by more than 2%" [1, p. 1007]. In support of these conclusions, the authors cite a US Department of Agriculture report that, they claim, "calculated that the US hog industry would have a net saving of $7 million if the use of antibiotic growth promoters ceased" [1, p. 1012]. But what the cited analysis actually says is that "Each producer is able to improve his or her net returns by feeding antimicrobial drugs. However, when all producers act in concert, feeding antimicrobial drugs, the collective result is to increase hog supplies; the increased supplies decrease hog prices" [2, p. 7]. Thus, this analysis supports the claim that feeding antimicrobial drugs to food animals (specifically hogs) expands supply and reduces prices; presumably, this is a significant finding for developing countries that desire these outcomes.

Similarly, the conclusion that "Poultry and pork production are unlikely to decrease by more than 2%" [1, p. 1007] appears to be a misreading of available data that only considers weight gain among animals rather than prevention of disease and mortality (and consequent loss of production) among animals raised without antibiotics. For example, since the antibiotic growth promoter bans were imposed in Europe, "Denmark, the world-leading pork exporter, has seen the number of pigs that die from illnesses increase by 25 percent over the past decade to about seven million animals a year. Of the 32 million pigs born in the Scandinavian country last year, 21.2 percent died…" [3, p. 1]. An increase in mortality rates from ~17% (prior to implementation of the animal antibiotic bans) to ~21.2% (after implementation of the bans) clearly represents a decrease in pork production of >2%.

Finally, Collignon and colleagues conclude that "Eliminating the routine use of in-feed antibiotics will improve human and animal health, by reducing the development and spread of antibiotic-resistant bacteria" [1, p. 1007]. However, sound risk management policy also requires consideration of whether eliminating in-feed antibiotics will harm human and animal health by increasing the spread of antibiotic-susceptible bacteria. Recent experience in Europe suggests that this is indeed the case, and quantitative modeling suggests that the potential harm to human health from increased microbial loads of susceptible bacteria may exceed the potential benefit to human health of a decreased prevalence of resistant bacteria by a ratio of >1000:1 [4]. Thus, prudent use of animal antibiotics may be effective in helping developing countries that seek safer, cheaper, more-plentiful meat supplies to achieve these goals.

Acknowledgments

Potential conflicts of interest. L.A.C. has previously received funds from the US Food and Drug Administration and the Animal Health Institute and its members for research on risk assessment of animal antibiotics and has testified for Bayer against the US Food and Drug Administration's withdrawal of enrofloxacin.

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Clinical Infectious Diseases 2006; 42:1053

Reply to Cox

SIR—We thank Dr. Cox for his interest in our article [1], but we disagree with his claims. As we have previously documented [1], all recent studies with adequate data and evaluation (in Europe, Brazil, and the United States) show that the economic benefits of in-feed antibiotics to the farming industry as a whole are marginal or nonexistent.

Dr. Cox [2] frequently quotes misleading figures regarding Denmark. Total antibiotic use in Denmark has decreased substantially, but there has been increased production in both pork and poultry since 1998 (when the routine use of in-feed antibiotics ceased). There has not been a 2% decrease in pork production, as Anthony Cox claims. The true figures can be easily checked in many independent sources [3–5]. Pork production increased from 1,520,600 metric tons in 1997 to 1,762,000 metric tons in 2004, which is a 16% increase [3]. Mortality, feed efficiency, and animal health issues have also been subjected to extensive scientific and economic reviews [4, 5]. The only support Anthony Cox gives for his incorrect claims is a press clipping [6].

Anthony Cox (usually in conjunction with funded lobby groups, such as the Animal Health Institute) has been prolific in preparing material used to lobby politicians, government officials, and the food industry. For instance, he argues that human campylobacter infections have almost nothing to do with poultry [2, 7]. Many of his statements have been shown to be false or misleading, not only in scientific journals, but also in administrative law proceedings [7, 8]. An entire section in a recent US Food and Drug Administration (FDA) determination was written about the unreliability of Cox's testimony [7], a finding made by both the FDA commissioner and an administrative law judge. Comments regarding his testimony included the following: "Dr. Cox's testimony lacked credibility and was unreliable," "He intentionally misquoted published articles," and "Dr. Cox's credibility was such that his testimony was so unreliable that it was inadmissible" [7, p. 16]. We suggest that readers who require additional details view these excerpts in the context of the Commissioner's final decision [7], particularly pages 16–17 and 108–119.

We are also concerned that some readers could misinterpret Anthony Cox's disclosed potential conflicts of interest in his letter. We understand that he has only done 1 small FDA consultation, which he completed 5 years ago (an undertaking that was controversial) [8]. He states this as his first conflict of interest and gives it equal weight to his association with the Animal Health Institute. However, he does not clarify that Animal Health Institute is a funded industry lobby group.

Dr. Anthony Cox's letter is another part of a well-funded, orchestrated campaign by certain sectors of the agriculture pharmaceutical industry that seek to protect indefensible practices. They continue to claim that the huge quantities of antibiotics added to animal feed do not result in antibiotic-resistant bacteria that spread to food, water, and people and cause harm, despite the overwhelming scientific evidence to the contrary.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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Clinical Infectious Diseases 2006; 42:1053–4

(1→3) β-D-Glucan Assay in the Diagnosis of Invasive Fungal Infections

SIR—Ostrosky-Zeichner et al. [1] have investigated the utility of the (1→3) β-D-glucan assay in the diagnosis of fungal infections using a case-control methodology. They report a sensitivity and specificity of 64.4% and 92.4%, respectively, with a positive predictive value (PPV) of 89% and a negative predictive value (NPV) of 73% when a cutoff value of 80 pg/mL was employed. Although the results of this study would appear to support the utility of this assay in diagnosing invasive fungal infections (IFIs), we question the choice of control patients and the presentation of predictive values.

The study included 163 patients with IFI (case patients) and 170 patients without IFI (control subjects). However, the case patients and control subjects were not matched for underlying disease status. No-

tably, 56.7% of control subjects were categorized as "healthy" or without underlying disease or risk factors, compared with 5.7% of case patients. We believe that this would likely impact the specificity and PPV reported. A control group matched for underlying disease is likely to approximate more closely the "real life" clinical setting in which the assay is used—in patients with risk factors for IFI (such as neutropenia), prolonged hospital and intensive care unit stay, prolonged antibiotic and corticosteroid exposure, central venous lines, and gastrointestinal surgeries. Such a control group might have included more patients who were receiving treatment modalities that have been associated with false-positive results in previous studies, including hemodialysis, immunoglobulin products, and glucan-containing colon gauze [2–4]. In addition, healthy control subjects are less likely to be heavily colonized with *Candida* species, compared with control subjects matched for underlying disease, a finding that has been associated with false-positive assay results in at least 1 study [5].

With respect to the presentation of PPV and NPV, the authors acknowledge that these values depend on the proportion of subjects sampled who are case patients (a quantity fixed by the investigators), but they do not give any indication of the degree to which these values change at different prevalence rates. On the basis of standard formulas relating predictive values to sensitivity, specificity, and prevalence, we have calculated the PPV and NPV from the sensitivity and specificity seen at the 60 pg/mL and 80 pg/mL cutoff values derived from this study and for a range of hypothetical prevalence values (figure 1). These curves illustrate that the PPV, in particular, can be heavily influenced by the prevalence of disease in the population. For example, at a (1→3) β-D-glucan cutoff value of 80 pg/mL, when the prevalence of disease is 49%, the PPV is 89% (as seen in table 3 of the study by Ostrosky-Zeichner et al. [1]). However, if the prevalence of disease were 20%—a liberal estimate for the types of infections being examined—the same sensitivity and specificities would yield a PPV of 68%. The presentation of PPV and NPV results from a population of selected case patients and unmatched control subjects does not provide useful information about the expected operating characteristics of the diagnostic test in the clinical setting in which it will be used.

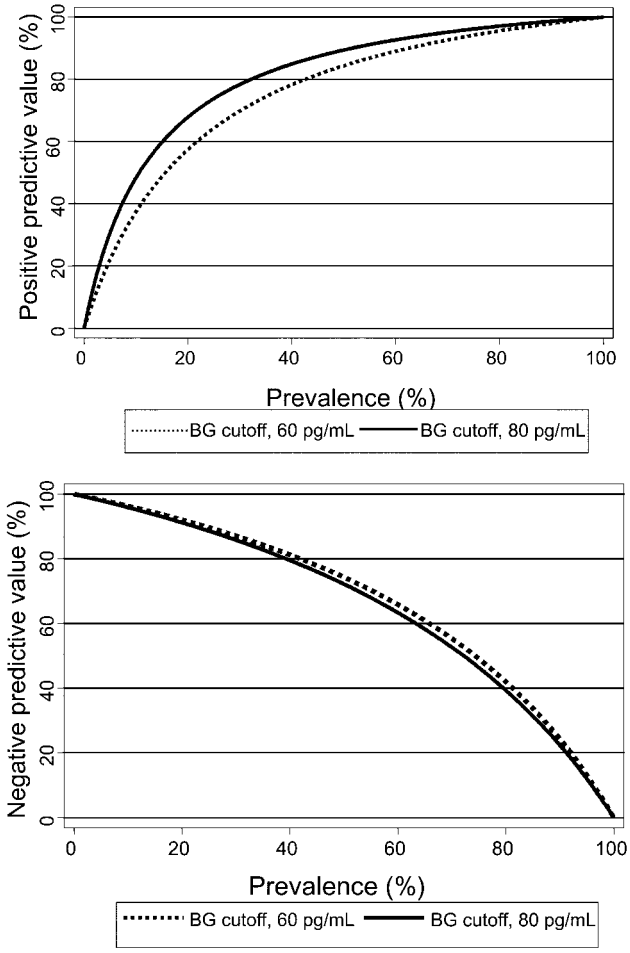

Figure 1. Positive predictive values (%) and negative predictive values (%) calculated from the sensitivity and specificity values reported with (1→3) β-D-glucan (BG) assay cutoff values of 60 pg/mL and 80 pg/mL [1], at a range of hypothetical prevalence values.

Acknowledgments

Potential conflicts of interest. K.A.M. has received research grant funding from Associates of Cape Cod. A.U. and W.L.: no conflicts.

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Clinical Infectious Diseases 2006; 42:1054–6

Reply to Upton et al.

SIR—We would like to thank Upton et al. [1] for reenforcing the limitations and statistical caveats we discussed in our recently published study regarding the use of (1→3) β-D-glucan as a diagnostic adjunct for fungal infections [2]. It is well known that the performance of a diagnostic test is intimately tied to prevalence of the disease in the studied population [3]. In our article [2], we stated that the prevalence of disease in our study may not reflect the prevalence of disease found in other specific settings.

However, we feel comfortable with our choice of control group, because we are working in a setting in which the test being investigated may be more sensitive than any other diagnostic test available at this time. We felt that it was important—at least for early validation of the test—to assure that we had subjects who definitely did not have fungal infection (such as the "healthy" subjects and a mix of subjects with other conditions that do reflect the circumstances in which the test is likely to be used) and subjects who did have proven fungal infection. Regarding the influence of *Candida* colonization, we would like to point out that the authors of the article to which Upton et al. [1] refer [4] conclude that *Candida* colonization was unlikely to be the cause of the false-positive results that they observed, because other patients in their study who had heavy colonization had negative results. Other authors have also failed to show any significant effects of colonization [5–7]. The curves created by Upton et al. [1] emphasize the need for judicious utilization of these markers, limiting their use to patients who are at high risk of fungal infection, a group in which the baseline incidence of invasive fungal infection will be higher; thus, the value of this test (and others) as an adjunct will be optimal [3].

Acknowledgments

Potential conflicts of interest. L.O.-Z. receives research grant support from Associates of Cape Cod. M.A.F. is an employee of Associates of Cape Cod.

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Clinical Infectious Diseases 2006; 42:1056

Effects of Selection of Control Subjects in a Case-Control Study on the Outcome of Catheter-Related Bloodstream Infection

SIR—More information on the attributable morbidity and mortality of catheter-related bloodstream infection (CR-BSI) is clearly needed. Until recently, only small case-control studies with limited power to exclude a clinically significant increase in morbidity or mortality were available. So, the large case-control study published by Blot et al. [1] in the 1 December 2005 issue of *Clinical Infectious Diseases* should provide us with important additional information on this topic.

However, there is 1 major methodological issue that requires clarification. Blot et al. [1] matched case patients and control subjects for duration of hospitalization (at the time of CR-BSI), for severity of illness (at admission to the intensive care unit [ICU]), and for disease category. This is the standard procedure in case-control studies that look for attributable mortality. But what I do not understand is why the control subjects were also not allowed to have a type of BSI other than CR-BSI. The authors write, in the subsection on setting and design, that "every ICU patient with CR-BSI was matched with 2 ICU patients who did not have evidence of bloodstream infection at any site during their ICU stay" [1, p. 1592]. This actually means that, when the authors were looking in their database for a matching control patient and ⩾2 control patients were found, a patient who also developed a secondary bacteremia (e.g., bacteremia caused by pneumonia, surgical site infection, or urinary tract infection) was not allowed to be a control subject. This bias in the selection of control subjects will, in my opinion, at least influence the cost of antibiotic use among the control patients, but it might also have other, more important consequences. For example, secondary bacteremia is associated with an increased hospital stay of 8 days [2]. Excluding control subjects with secondary bacteremia will, therefore, result in a shorter ICU stay and

also possibly a better overall outcome among the control subjects, compared with the case patients. In my opinion, only CR-BSI should have been disallowed in control subjects.

Acknowledgments

Potential conflicts of interest. B.J.A.R.: no conflicts.

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Clinical Infectious Diseases 2006; 42:1056–7

Reply to Rijnders

Sir—We appreciate the thoughtful remarks by Dr. Rijnders [1] regarding our article [2]. In his letter, the method of selection of control subjects in our matched cohort study is questioned. Dr. Rijnders [1] suggests that the a priori exclusion of control subjects with secondary bloodstream infection (BSI) could have resulted in a bias leading to a shorter median intensive care unit stay and a lower cost of antibiotics for patients in the control group.

In our study, control subjects were taken from a pool of patients without documented nosocomial BSI. As a consequence of this exclusion, control subjects were a priori free of BSI, although such an infection in a control patient would have been acceptable from a methodological viewpoint. To avoid confounding bias, patients with catheter-related BSIs (case patients) were not allowed to have a secondary BSI during their intensive care unit stay apart from their catheter-related infection; our matched cohort analysis was primarily designed to estimate the impact of catheter-related BSI. Because matching was done on the basis of severity of acute illness and underlying disease, diagnostic category, and exposure time, we can assume that the prevalence of intensive care unit–acquired infection without BSI was similar between case patients and control subjects. Thus, by excluding patients with secondary BSI from both case and control groups, as well as by instituting strict matching criteria, the load of infectious diseases among case patients and control subjects is probably well balanced.

Although excluding control patients with a secondary BSI theoretically could have led to an underestimation of the cost and length of stay for persons in the control group, this effect is probably very limited. Given the low prevalence of nosocomial BSI among our intensive care unit population, patients with a secondary BSI, if allowed to participate, would have formed only a small minority of the control population. To illustrate this, 6 (3%) of 192 case patients were effectively excluded because of a secondary BSI. Because case patients and control subjects were matched for disease severity and risk profile, it can be assumed that the prevalence of such infection would be similar in both groups. Assuming that we were to perform the study without the aforementioned restriction, it could be expected that 3% of the control group would have had a secondary BSI. Among the 315 control subjects of the present study, this would have translated to 9 control patients with secondary BSI. It is rather unlikely that such a small number of patients would have changed the final conclusion regarding the economic impact of catheter-related BSI.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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Clinical Infectious Diseases 2006; 42:1057

Successful Treatment of *Legionella maceachernii* Pneumonia after Diagnosis by Polymerase Chain Reaction and Culture

Sir—Pneumonia due to *Legionella maceachernii* has rarely been described. So far, all described patients with this infection have died [1]. We diagnosed a case of *L. maceachernii* pneumonia by PCR. It was subsequently confirmed by culture, and the patient responded favorably to treatment with ciprofloxacin.

A 53-year-old man who had undergone a liver transplantation 2 years earlier was admitted to our hospital 2 days after returning from a 1-month-long trip to the Dominican Republic. Because of acute gastroenteritis, the patient had interrupted his immunosuppressive medication, which had led to acute rejection, for which he was treated with high-dose methylprednisolone. Two days after his hospital admission, he developed fever with a temperature up to 39°C. He had been coughing for some weeks and had experienced mild dyspnea during exercise. He also had jaundice and mild tachypnea. Laboratory tests showed leukocytosis (leukocyte count, 12.8×10^9 cells/L), an elevated creatinine level (122 μmol/L), and elevated liver enzyme and bilirubin levels (aspartate aminotransferase level, 57 IU/L; alanine

aminotransferase level, 142 IU/L; alkaline phosphatase level, 300 IU/L; γ-glutamyl transferase level, 463 IU/L; total bilirubin level, 183 μmol/L; and conjugated bilirubin level, 128 μmol/L). His chest x-ray showed an infiltrate of the anterior segment of the right upper lobe (figure 1). Empirical therapy was started with ciprofloxacin (dosage, 400 mg twice daily). The results of a urinary antigen test for *Legionella pneumophila* were negative. A bronchoalveolar lavage fluid specimen was positive by a real-time PCR that detected all strains belonging to the genus *Legionella,* but negative by a PCR specific for *L. pneumophila* [2]. Because the sample was positive at cycle 25, this suggested a large amount of *Legionella* DNA in the sample. The major part of the eubacterial 16S rDNA was amplified with universal primers [3]. The nucleotide sequence revealed a homology of 98.8% (1433 of 1451 base pairs were identical) to the *L. maceachernii* (AF227161) sequence. Notably, the findings of a throat swab were negative with the *Legionella* species PCR. The patient was treated for 3 weeks, at which time he could leave hospital without dyspnea, tachypnea, or cough. The results of his renal and liver function tests were not normal by then, but we assumed that the increased values of these tests were unrelated to the *Legionella* species infection.

Since the initial culture result of the bronchoalveolar lavage fluid specimen was negative for *Legionella* species, a sample that initially had been stored at −20°C was recultured on buffered charcoal yeast extract plates with and without antibiotics (polymyxin, anisomycin, and cefamandole). During the second week of incubation, a few colonies of *L. maceachernii,* confirmed by sequence analysis of the 16S rRNA, grew on buffered charcoal yeast extract plates, but not on plates with antibiotics, because *L. maceachernii* is susceptible to cephalosporins [4]. As tested by disk diffusion, the strain was sensitive to erythromycin and ciprofloxacin.

L. pneumophila causes >90% of all *Legionella* infections [5], and *Legionella micdadei, Legionella longbeachae, Legionella bozemanii,* and *Legionella dumofii* are the most commonly encountered non–*pneumophila* species of *Legionella.* Because the results of the urinary antigen test are negative in patients with infection caused by non–*pneumophila* species of *Legionella,* strains are easily overlooked in culture, and serological examination is an unreliable tool to detect these infections, the infections are probably underdiagnosed. Without the availability of PCR, our patient's infection would not have been diagnosed. In studies in which PCR is used, up to 8% of samples have been reported as positive in community-acquired pneumonia [6].

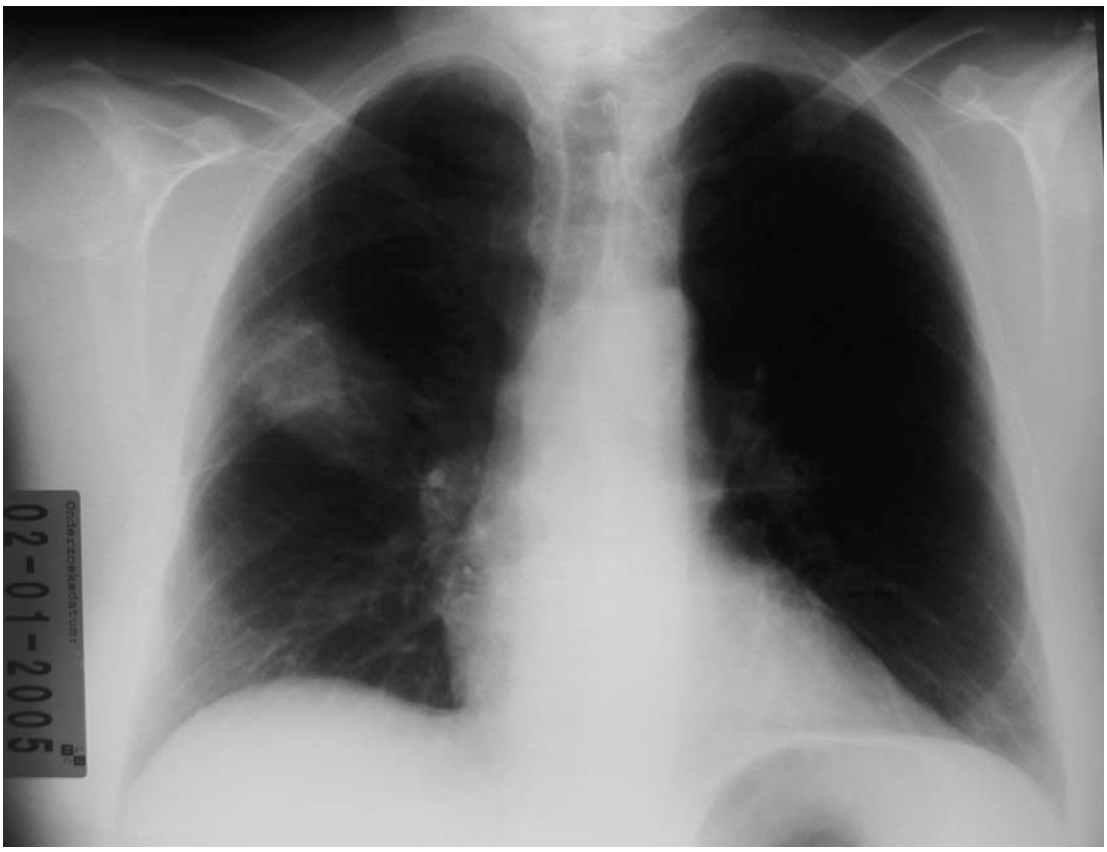

Figure 1. A chest x-ray of the patient at hospital admission shows an infiltrate in the anterior segment of the right upper lobe

However, positive PCR results for non-*pneumophila* species of *Legionella* can also be caused by environmental contamination of the specimen [7]. Therefore, for diagnosis of infections due to non-*pneumophila* species of *Legionella,* culture remains, in our view, the gold standard. Using real-time PCR, a low threshold cycle value is probably also indicative of infection, but this should be investigated in more detail.

Only 4 cases of *L. maceachernii* pneumonia have been described so far [1]. Three patients lived in North America and 1 in Australia. Because our patient probably acquired the infection in the Dominican Republic, it is not certain whether *L. maceachernii* is endemic in Europe. All patients whose cases have been published had underlying disorders, such as HIV infection, multiple myeloma, systemic lupus erythematosus, and autoimmune hemolytic anemia, and 2 of them used prednisone. All patients died; therefore, our patient is the first documented patient to survive this disease.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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Clinical Infectious Diseases 2006; 42:1057–9

Coccidioidomycosis in HIV-Infected Persons

Sir—I would like to comment on the article by Dr. Neil Ampel [1] regarding coccidioidomycosis in HIV-1–infected persons. Dr. Ampel notes that there are data suggesting a decrease in the incidence of symptomatic coccidioidomycosis in persons with HIV infection since the advent of HAART. Although this is true, I would like to share data from my clinic, located in Tucson, Arizona, regarding all-cause mortality in the HAART era. El Rio Special Immunology Associates is a community health center–based clinic that is funded by the Ryan White Comprehensive AIDS Resources Emergency Act, and it is the largest provider of HIV primary care in southern Arizona, with ~1500 persons receiving care. A review of our mortality data reveals that 29 of 116 deaths that occurred between 1 January 2001 and 31 December 2004 were caused by coccidioidomycosis. Despite the advent of HAART, coccidioidomycosis remains the leading cause of death at our clinic, accounting for fully 25% of deaths.

My observation is that these deaths can be divided into 2 categories. The first is composed of persons with fulminant pulmonary disease who are either unaware of their HIV infection or who have chosen not to receive HIV treatment. The second group is composed of HIV-positive persons with chronic infection, generally of the CNS, who ultimately experience treatment failure. Although this treatment failure is frequently attributable to nonadherence, it is my observation that, even in persons who have sustained good immune system recovery (defined as an increase in CD4 cell count to levels >200 cells/mm^3), there remains a risk of relapse and death due to CNS infection. Consequently, it is the practice of myself and my associates at El Rio Special Immunology Associates never to discontinue azole therapy in persons with disseminated infection, even in the face of improved CD4 cell counts.

Lastly, I believe there is an error in the article with regard to voriconazole. Although it is a powerful antifungal, the use of voriconazole by HIV-infected persons is limited by its drug interactions. Efavirenz and ritonavir are both contraindicated for use with voriconazole [2].

Acknowledgments

Potential conflicts of interest. J.K.C.: no conflicts.

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Clinical Infectious Diseases 2006; 42:1059

Reply to Carmichael

Sir—Regarding Dr. Carmichael's comments [1] about my recent article on coccidioidomycosis during HIV infection [2], I agree that, for HIV-infected persons living in an area where the disease is endemic who are not receiving potent antiretroviral therapy, severe coccidioidomycosis will remain a significant risk if their peripheral

CD4 cell count is <250 cells/μL. With regard to CNS disease, coccidioidal meningitis has been previously observed as a common manifestation of dissemination among HIV-infected patients with severe immunosuppression [3, 4].

As Dr. Carmichael's [1] experience indicates, all patients with disseminated coccidioidomycosis who stop azole therapy are at risk for relapse, regardless of HIV infection status. For non-meningeal disease, relapse occurs in 15%–30% of patients [5–7] and is seen in nearly 80% of those with coccidioidal meningitis [8], prompting the recommendation that azole therapy for meningitis be lifelong [9]. As stated in my article [2], prolonged or even lifelong therapy should be considered for all persons with disseminated coccidioidomycosis and HIV infection.

I appreciate Dr. Carmichael personally contacting me regarding voriconazole interactions. This omission has been corrected in a published erratum [2].

Acknowledgments

Potential conflicts of interest. N.M.A.: no conflicts.

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Clinical Infectious Diseases 2006; 42:1059–60
 1058-4838/2006/4207-0035