

Correspondence

Ad Hominem Argument Unsuitable for Animal Antibiotics

TO THE EDITOR—I recently questioned [1] the interpretation by Collignon et al. [2] of a US Department of Agriculture study [3] that they cited in support of their contention that, as they state in their title, “The Routine Use of Antibiotics to Promote Animal Growth Does Little to Benefit Protein Undernutrition in the Developing World” [2]. The US Department of Agriculture study actually indicates that feeding antimicrobial drugs as growth promoters to hogs both expands supply and reduces prices [3]. In their response to my letter [1], Collignon et al. [4] did not address my question about their interpretation of the US Department of Agriculture study [3], but instead, engaged in an inaccurate and inappropriate ad hominem attack. They quoted an administrative law judge (an employee of the US Food and Drug Administration [FDA]) attacking the credibility of my testimony against the FDA in an unrelated 2003 case that did not involve growth promoters. That case dealt with resistance risks associated with the use of the therapeutic drug enrofloxacin. This was not the topic of my correspondence. Although Collignon et al. [4] declared “no conflicts,” Dr. Wegener was, in fact, a witness for the FDA in that litigation [5].

Although I strongly disagree with the positions ascribed to me by the FDA and its witnesses in the context of that litigation [6], referred to and quoted by Collignon et al. [4], I believe that interested readers can decide for themselves the technical merits of that case based on peer-reviewed publications [7, 8]. In contrast, I believe that the response by Collignon et al. [4] contains many false claims that a reader cannot easily check. The purpose

of this letter is, therefore, to identify what I perceive as important factual inaccuracies in the reply of Collignon et al. [4]. These include the following points.

The statement that “Dr. Anthony Cox’s letter is another part of a well-funded, orchestrated campaign” [4, p. 1054] is untrue and unfounded. My letter was unfunded, was not part of any larger effort, and was not coordinated with, orchestrated by, or solicited by anyone else. Similarly, it is not true that my research and publications in this area are carried out “usually in conjunction with funded lobby groups” [4, p. 1054].

The claim that “Many of [my] statements have been shown to be false or misleading, not only in scientific journals, but also in administrative law proceedings” [4, p. 1054] is also untrue. The citations given by Collignon and colleagues are *not* to scientific journals, but to non-peer-reviewed statements made by the FDA [6] (with which I strongly disagree) in the same Baytril (Bayer) litigation. My work criticizing the FDA’s reasoning and risk analysis of Baytril [7, 8] has not been refuted in any journal articles that I have seen.

It is false and misleading to state that I argue “that human campylobacter infections have almost nothing to do with poultry” [4, p. 1054]. To the contrary, I have calculated that “6660 estimated excess campylobacteriosis cases per year in the base case” [9, p. 549] is a plausible *lower-bound* estimate of the human health effects of campylobacteriosis from eating chicken if antibiotics are not used. I have written that the true number may well be even larger, consistent with recent experience in Europe [8, 9].

Collignon et al. [4] claim that I give my work for FDA “equal weight” to my association with the Animal Health Institute. Although the work that I did for the FDA

came before my work for Animal Health Institute and awoke me to the urgent need to develop better methods of risk analysis in this area [8], my disclosure clearly states that I have testified *against* the FDA; thus, readers need be in no doubt about my prior work. (Indeed, if we all used the same standards of disclosure, it might have been appropriate for the authors of the response to have mentioned that Dr. Wegener’s work was used *for* the FDA in the same case, [10], and their work has frequently been used to lobby *for* banning animal antibiotics.)

I agree with Collignon et al. [4] that my letter cited a recent press publication (although other, less-recent references regarding the decline of health in pigs in Denmark following the bans are readily available [11]), and acknowledge that it would be more accurate to say that *productivity* decreased by more than 2%, rather than that *production* decreased by more than 2%. The 2 terms are equivalent under the normal *ceteris paribus* assumptions of economic analysis when the other inputs to the production process remain fixed. Nonetheless, the validity of the observed increase in mortality in Danish pigs remains unchallenged and unexplained by Collignon and colleagues.

In summary, the response by Collignon et al. [4] to my letter [1] did not address the main scientific point made in the title of my letter; rather, they mounted a sustained ad hominem attack that included statements I consider to be unsupported, misleading, and abundantly untrue. The practice of using personal attacks instead of reasoned discussion deserves no place in a scientific journal. It is time to restore comity and composure to this discussion and to refocus attention on key technical and factual issues, such as what conclu-

sions are actually warranted by cited data sources.

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Treatment of Shiga-Like Toxin-Producing *Escherichia coli* Infection

TO THE EDITOR—The findings of Bennish et al. [1], with regard to a reduction in the frequency of hemolytic uremic syndrome (HUS) among patients who received appropriate antibiotics for *Shigella dysenteriae* infection, should resurrect interest in designing a prospective antibiotic treatment trial for enterohemorrhagic *Escherichia coli* (EHEC) infection. As the authors detail, Shiga toxin is analogous to one of the common Shiga-like toxins, which are produced by EHEC. Furthermore, there is considerable phylogenetic similarity between *E. coli* and *Shigella* species. Both of these factors enhance the theoretical potential that EHEC infections could be benefited by similar treatments, including antimicrobial chemotherapy.

As I have previously suggested [2], the choice of antibiotic is critical, because previous studies have shown that, despite in vitro susceptibility, only certain antibiotics are effective for shigellosis [3]. Wong et al. [4] proposed that antibiotics may be a risk factor for progression to HUS during EHEC infection, but the stratification and categorization of antibiotic use would not be consistent with shigellosis treatment trials.

A recent meta-analysis from Safdar et al. [5] did not find an increased risk of HUS in EHEC infection. Data from Bell et al. [6] and Proulx et al. [7] also provide similar findings. The latter studies complement those by my colleagues and me [8], in which the safety of certain antibiotics for treatment of *E. coli* O157:H7 infection was proposed. In other research, we found a possible protective effect of

particular antibiotics [9, 10]. Although these studies are not definitive with regard to safety and protection, they, along with the supportive findings of Bennish et al. [1], provide plenty of fuel for hypothesis testing. It is justifiable to propose that an advance in treatment is possible.

Caution in the use of antimicrobial chemotherapy is justified, but such caution should not jeopardize the execution of prospective, randomized treatment trials. A choice of ampicillin for the therapeutic trial would be preferable, given the theoretical risk of complicating an evolving nephropathy with a relatively insoluble sulfonamide combination. The treatment group would ideally include children of young age who are at greater risk for progression to HUS and children who are seen early in the course of the illness. The randomized design would necessarily include a preconceived number of patients to achieve sufficient power, but the randomized code and the interim results could be available to an independent oversight group, which would ensure that the study be terminated if preliminary data showed an obvious trend towards adverse effects of antibiotic treatment. The time has come to move forward.

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Enterobacterial Repetitive Intergenic Consensus–Polymerase Chain Reaction for Typing of Uropathogenic *Escherichia coli* Is Not What It Seems

TO THE EDITOR—France et al. [1] report studies of clonal relationships between antimicrobial-resistant uropathogenic *Escherichia coli* (UPEC) using enterobacterial repetitive intergenic consensus (ERIC)–PCR and other typing techniques. Previously, Manges et al. [2, 3] reported a related group (clonal group A) of *E. coli* associated with urinary tract infection. In subsequent correspondence, there was discussion of the limited reproducibility of ERIC-PCR [4–6]. We also have studied ERIC-PCR as part of an investigation of relationships between UPEC in our region. We included *E. coli* ATCC 25922 and

E. coli K12 as controls in each PCR run. PCR products were obtained from K12 and ATCC 25922; however, there was a great deal of variability with respect to the patterns obtained in 3 consecutive PCR runs performed by the same operator with the same lot of template DNA, reagents, and thermal cycler. This experience is consistent with those reported in recent correspondence and by Meacham et al. [4–7]. This prompted us to review the basis of ERIC-PCR typing.

ERIC sequences are highly conserved 126–base pair (bp) noncoding regions that are repeated multiple times through the bacterial genome. The location of ERIC sequences varies from strain to strain [7, 8]. In 1991, Versalovic et al. [9] reported ERIC-PCR typing. This method is based on the expectation that complementary oligonucleotides will anneal to ERIC sequences and that the DNA between the ERIC sequences may be amplified, provided that the interval between ERIC sequences is <5 kilobases. Because there are multiple ERIC sequences, there is potential for amplification of multiple PCR products. Variation in the number and location of ERIC sequences between unrelated strains of *E. coli* is expected to result in differences between strains in the number and size of PCR products. Differences in the number and size of PCR products result in differences in banding patterns when the products are separated by electrophoresis. The Web site of the Pasteur Institute [10] indicates that there are 21 ERIC sequences in the sequenced *E. coli* K12 genome, which we used as a control. It is apparent from this sequence, which was not available in 1991, that the smallest interval between 2 ERIC sequences in *E. coli* K12 is 42,404 bp. This interval is far beyond the range of amplification of conventional PCR and much greater than the size of products identified on ERIC-PCR gels [1]. We believe that the theoretical basis for ERIC-PCR, which has become important in the investigation of the clonal relationships between UPEC, is flawed. Given the interval between ERIC

sequences, at best, one can anticipate that one of the primers related to each product generated in an ERIC-PCR run anneals to an ERIC sequence, with another copy of the primer annealing to a partial sequence match under low stringency (50°C) annealing conditions. ERIC-PCR may be considered to be a variant of random amplification of polymorphic DNA–PCR, which also lacks reproducibility. The flawed basis of ERIC-PCR explains the lack of reproducibility of the technique and adds emphasis to calls for caution in the interpretation of results based on this method.

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***Plasmodium falciparum* Chloroquine-Resistance Transporter Gene Detection in Imported *Plasmodium falciparum* Malaria Cases**

TO THE EDITOR—We share the cogent sentiments expressed by Farcas et al. [1] about the great interest of PCR-based methods for the diagnosis of imported malaria, given that, in most westernized countries, morbidity and death due to this protozoan infection among returned travelers is on the rise [2]. Because we have tested >900 patients per year since October 1999, we have accumulated a large amount of routine experience in the molecular diagnosis of imported malaria. First using conventional PCR [3], and now using real-time PCR [4], we have found that the detection of mixed-species infections was sharply improved by both techniques. Overall, however, real-time PCR demonstrates a decisive feature for our clinician colleagues: the capacity to ensure, in a turnaround time of <4 hours, 6 days a week, that a given febrile traveler does not have malaria.

In addition to its utility in the diagnosis of malarial infection, PCR appeared to be a must for epidemiological surveys focused on *Plasmodium falciparum* with resistance to aminoquinolines, as assessed by the detection of point mutations in the *P. falciparum* chloroquine-resistance transporter (*pfcr*) and *P. falciparum* multidrug-resistance (*pfmdr1*) genes. Performed in cohorts of returned travelers or immigrants, such molecular surveillance studies showed that a large proportion of patients (1%–3%) who presented with falciparum malaria harbored the K76 (wild-type) *P.*

falciparum strain [5, 6]. In other words, the malarial infections of these subjects probably would have been cured by chloroquine (CQ), which remains one of the cheapest and safest drugs ever used for malaria treatment. So, we are in full agreement with Farcas et al. [1], who claimed that the molecular assessment of CQ sensitivity, based on the detection of T76 mutation by real-time PCR, appeared to offer an interesting perspective, as previously suggested in a review article [7].

In this view, the sensitivity of a molecular test for the detection of CQ resistance would be of crucial importance. That is, such an assay should display good absolute sensitivity, but it should also be able to detect a minority mutant fraction in a sensitive wild-type population. The test performed by Vessièrè et al. [8] in the Department of Parasitology (Rangueil University Hospital, Toulouse, France) exhibited 2% sensitivity for the detection of the K76T mutation, which appeared to be insufficient to avoid the occurrence of RI/RII resistance in the event of therapeutic use of CQ. We therefore developed a more sophisticated assay, in which locked nucleic acid probes blocked the amplification of wild genotypes, so that the detection of mutated parasites was boosted. As a result, the sensitivity peaked at 0.063%, translating to 1 mutated *P. falciparum* parasite of 1600 wild-type *P. falciparum* asexual forms [9]. Given the design of both primers and probes, this PCR assay could detect all K76T *pfcr* haplotypes, and it provided 2 different melting temperature points (T_m), 1 for mutated and 1 for wild-type haplotypes. Thus, the result was not affected by the geographical origin of the parasite isolate [1].

We were, therefore, surprised that Farcas et al. [1] did not assess the sensitivity of their method using, for example, artificial admixtures of mutated and wild *P. falciparum* strains. Moreover, these authors did not find any mixed infection (infection with wild-type and mutated strains) among 200 isolates studied [1]. In

comparison, Vessièrè et al. [8] reported 11 of 131 imported malaria cases were mixed infections, most of African origin. By locked nucleic acid PCR, 21 mixed infections were detected in the same batch of patients (A. Berry, personal communication). A specificity problem could be excluded, because none of these 11 or 21 patients had positive results for malaria by both conventional and real-time PCR techniques for a species other than *P. falciparum*. Because Farcas et al. [1] did not give any description of the primers they used, any analytical comparison with our studies was impossible. The sensitivity level of their assay remains, therefore, questionable, which is a pending problem for a kit that could have a commercial destiny.

Farcas et al. [1] criticized the assay used by Vessièrè et al. [8] because of “the lack of head-to-head comparison with an accepted reference standard” [1, p. 626]. As far we know, there is no available “reference standard” for the K76T mutated *P. falciparum* strain; moreover, we did not find any use for such a standard in Farcas and colleagues’ article. Concerning “the lack of negative controls” [1, p. 626], we will refer back to figure 1 in Vessièrè and colleagues’ article, in which an admixture containing 0% of mutated parasites was used as a negative control.

Finally, we fully agree with Farcas et al. [1] about the need for high-quality requirements in laboratories performing malaria diagnosis. In France and in most countries in the European Union, any private or public laboratory must implement Good Laboratory Practices, a minimal legal obligation. However, far more rigorous quality constraints should be expected from specialized laboratories handling molecular techniques for routine diagnosis of infectious diseases. Our department is in the process of completing accreditation by the French Committee for Accreditation, the French branch of the International Accreditation Forum [10]. Under review are the molecular diagnostic procedures for malaria (including the de-

tection of K76T mutation), for cutaneous and visceral leishmaniasis, for pneumocystosis, and also for in utero toxoplasmosis. Within the next 2 months, the practices of the Molecular Diagnostic Unit (Rangueil University Hospital, Toulouse, France) will be compliant with the International Organization for Standardization 17025:2005 and 9001:2000 standards.

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A Simple Algorithm for the Diagnosis of AIDS-Associated Genitourinary Tuberculosis

TO THE EDITOR—As has been shown in surveys in Canada, the United Kingdom, and the United States, genitourinary tuberculosis (TB) is a common form of nonpulmonary TB, accounting for 27% (range, 14%–41%) of the extrapulmonary TB cases [1]. Among patients with AIDS, the incidence of genitourinary TB may be even higher. In an autopsy study in India, 24 of 35 kidneys from patients who died of AIDS showed evidence of infection, including 17 cases of TB [2]. In a similar study in Mexico City, renal disease was demonstrable in 87 (63%) of 138 autopsies performed on patients with AIDS; infection was the cause of the renal disease in 36 cases, with 19 being due to *Mycobacterium tuberculosis* [3]. However, no data of the prevalence of genitourinary TB in living patients with AIDS can be found in the literature. TB of the urinary tract is easily overlooked. The disease is very slow to progress, with minimal and subtle symptoms, and the signs and symptoms mimic those of other infections of the kidney [4].

The prevalence of TB in Venezuela is moderate (27 cases per 100,000 inhabitants), and genitourinary TB is hardly diagnosed in our patients with AIDS. From 2001 to September 2003, only 2 cases of TB were detected in our 600-bed hospital. To determine the prevalence of TB of the

urinary tract among hospitalized patients with AIDS in our hospital, we applied a simple algorithm based on the absence of positive results of culture on routine media for patients with AIDS and pyuria, albuminuria, or hematuria in the urine examination. Patients with a diagnosis of pulmonary or extrapulmonary TB were excluded from this study. Of 88 patients classified as having AIDS category C [5] and being hospitalized between September 2003 and December 2004, 22 patients with sterile pyuria, albuminuria, or hematuria had a urine examination and received a diagnosis of TB of the urinary tract. Three overnight urine samples that were neutralized with bicarbonate were obtained from each patient. The samples were centrifuged, and a slide was prepared for Ziehl-Neelsen staining, and, posterior to decontamination with 2% NaOH, the samples were inoculated on 2 L-J slants. Urine samples for 6 patients (27%) were positive for acid-fast bacteria (2 by smear examination and culture and 4 by culture only). All isolates were identified as *M. tuberculosis* using standard techniques. The patients—5 men and 1 woman—had a mean age of 39.1 years (SD, ±6.2 years). Albuminuria was the most common laboratory abnormality (5 of 6 patients), followed by pyuria (4 of 6 patients) and hematuria (3 of 6 patients). None of the patients had positive skin test results. One patient had an abnormal chest radiograph, but no pulmonary TB was diagnosed on processing of 3 sputum samples. In addition, another patient received a diagnosis of lymph node TB when his urine culture became positive for *M. tuberculosis* 4 weeks later. We conclude that genitourinary TB is very common among our patients with AIDS and that an algorithm based on a simple urine examination has a very high predictive value for the diagnosis of genitourinary TB and should be included in the differential diagnosis of patients with AIDS and sterile pyuria, albuminuria, or hematuria.

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Cytomegalovirus Disease in HIV Infection: Twenty Years of a Regional Population's Experience

TO THE EDITOR—More than 50% of the adult population worldwide is latently infected with human cytomegalovirus (CMV) [1]. Individuals with human immunodeficiency virus (HIV) infection and CD4⁺ cell counts <100 cells/mm³ are at significant risk for CMV reactivation leading to invasive disease [1, 2]. Our objectives were to characterize the incidence, clinical features, and outcome of CMV disease in a geographically defined, HIV-infected population between 1984 and

2005. The study period was divided into the pre-HAART era (1984–1996) and the HAART era (1997–2005).

Data for a total of 2655 adults (CMV seropositivity rate, 93%) with 9417 person-years of HIV follow-up care (3452 person-years during the pre-HAART era and 5965 person-years during the HAART era) were reviewed. A total of 169 patients developed CMV disease (143 patients during the pre-HAART era and 26 patients during the HAART era). In 166 patients, disease was attributable to reactivation of latent CMV infection, whereas in 3 patients, disease developed following documented CMV seroconversion. CMV disease was seen in 92% of patients with CD4⁺ cell counts ≤100 cells/mm³ (median CD4⁺ cell count, 16 cells/mm³).

The introduction of HAART, which has increased the mean CD4⁺ cell count of our population (mean CD4⁺ cell count in the pre-HAART era, 390 cells/mm³; mean CD4⁺ cell count in the HAART era, 432 cells/mm³; *P* < .001, by analysis of variance), has reduced the proportion of pa-

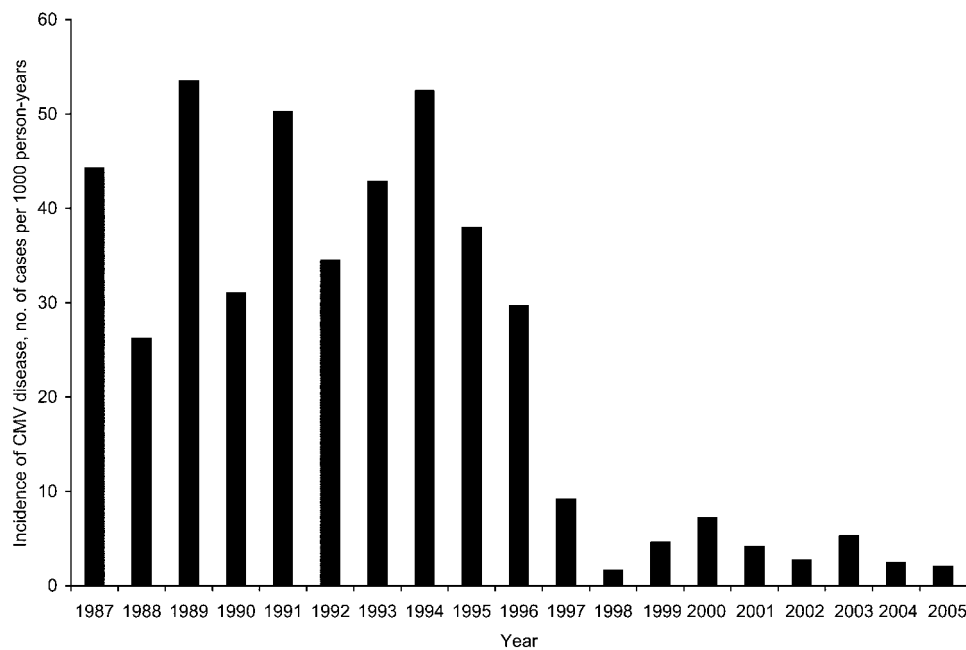


Figure 1. Annual incidence of cytomegalovirus (CMV) disease among the southern Alberta population of HIV-infected individuals, 1987–2005. The introduction of HAART was immediately followed by a drastic decrease in the incidence of CMV disease among the HIV-infected population of southern Alberta (*P* < .001, by nonpooled Student's *t* test). There were 4 diagnoses of CMV disease among 15 patients receiving care in 1986 (542 cases of CMV disease per 1000 person-years); this data was omitted for clarity.

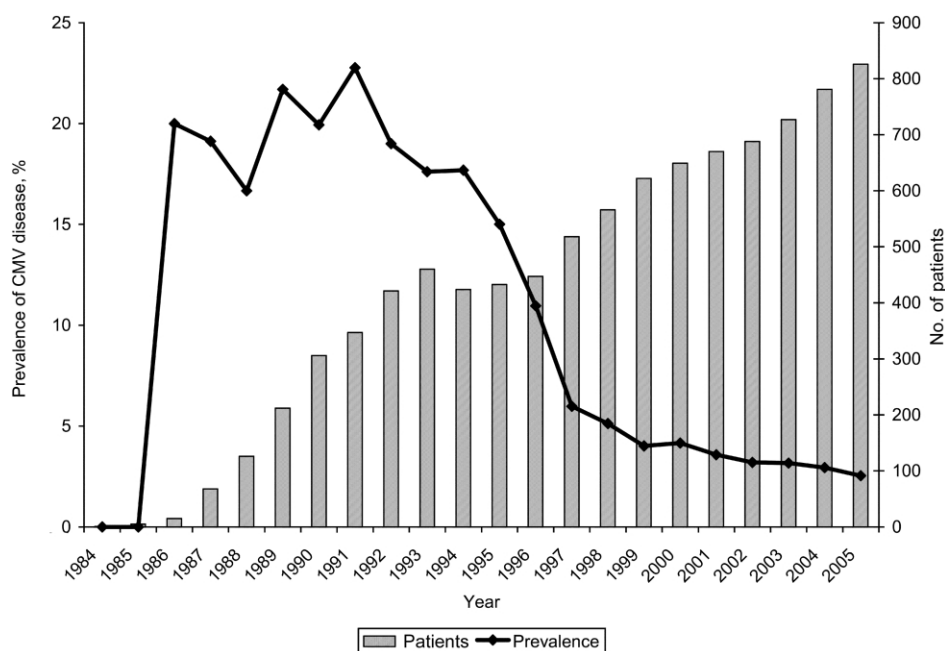


Figure 2. Prevalence of cytomegalovirus (CMV) disease among the southern Alberta population of HIV-infected individuals, 1984–2005. The prevalence of CMV disease has remained relatively stable at 4% during the HAART era ($P < .001$, by nonpooled Student's *t* test), despite an increasing number of HIV-infected individuals receiving care for HIV infection at the Southern Alberta Clinic (Calgary, Alberta, Canada).

tients at risk for reactivation of CMV disease. More than 21% of all clinic patients had a CD4⁺ cell count ≤ 100 cells/mm³ in the pre-HAART era, compared with 8% in the HAART era ($P < .001$, by nonpooled Student's *t* test). The incidence of a first episode of CMV disease decreased from a mean incidence of 40 cases per 1000 person-years during the pre-HAART era to 4 cases per 1000 person-years during the HAART era ($P < .001$, by nonpooled Student's *t* test) (figure 1). The prevalence of CMV disease among our population has decreased from 15% in the pre-HAART era to 4% in the HAART era ($P < .001$, by nonpooled Student's *t* test) (figure 2). The mean mortality rate primarily associated with CMV disease has decreased from 178 to 27 deaths per 1000 person-years with the use of HAART ($P < .05$, by nonpooled Student's *t* test).

Despite the availability of HAART, 4 cases of CMV disease per 1000 person-years of HIV follow-up care still occurred. These cases were seen in patients with a median CD4⁺ cell count of 13 cells/mm³ and a median HIV load of 181,156 copies/

mL who either presented for initial HIV care with a severely damaged immune system or had a known HIV infection and either poor adherence to HAART or drug-resistant HIV.

We have shown how, in a well-defined, HIV-infected population, the use of HAART was associated with a decreased number of individuals with sustained low CD4⁺ cell counts at risk for CMV disease. A concurrent decrease in the incidence, morbidity, and mortality associated with CMV disease was documented. CMV disease, however, was still seen. Patients with severely damaged immune systems who either presented for HIV infection care or who had adherence or intolerance issues, had multidrug-resistant HIV infection, or refused HAART accounted for these new cases. Given that well over 90% of HIV-infected patients are seropositive for CMV infection and that increasing numbers of patients are exhausting HAART options and experiencing decreases in CD4⁺ cell counts, the ongoing threat of CMV disease must not be overlooked.

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Brain Abscess Due to *Arcanobacterium haemolyticum* after Dental Extraction

TO THE EDITOR—It has been suggested that 5%–20% of brain abscesses are presumably associated with oral infections or dental procedures [1–4], in which organisms belonging to the oropharyngeal flora, such as *Arcanobacterium haemolyticum*, are involved [5, 6]. This organism has been documented in cases of pharyngitis and wound infections [7], but rarely in systemic infections [7–9] and even less in brain abscesses [10]. We describe the case of a patient who developed a brain abscess due to *A. haemolyticum* infection after undergoing dental extraction procedure.

An 18-year-old man without a remarkable medical history, except for repeated periodontal manipulations, was admitted to the hospital with headache, vomiting, aphasia, weakness in his left extremities, behavior and mood alterations, and fever. Three months before admission, he had been treated for periodontitis and dental caries in a primary dental clinic. He underwent extraction of multiple teeth. He had been well until 15 days before hospital admission, when intense headache and vomiting developed. Seven days before hospitalization, weakness in his left extremities became worse, and he was unable to stand or walk. A brain CT scan revealed a left-sided hypodense fronto-parietal lesion with cystic, contrast ring enhancement and perilesional edema exerting a significant mass effect (a 1.8-cm displacement of the middle line). He was referred to our hospital and was admitted to a neurosurgical ward. On admission to the neurosurgical ward, he was afebrile. His blood pressure was 140/80 mmHg, his respiratory rate was 14 breaths per min, his heart rate was 82 beats per min, and his temperature was 36.6°C. He was conscious and alert. Neurologic examination revealed no evidence of neck stiffness or of Kernig's or Brudzinski's signs. Muscle strength was 3/5 in his left leg muscle and in his left forearm muscle. Laboratory data included a peripheral WBC count

of 19.02×10^9 cells/L with 88% neutrophils, a hemoglobin level of 13.3 g/dL, a platelet count of 304×10^9 platelets/L, and an erythrocyte sedimentation rate of 10 mm/h. His aspartate aminotransferase, alanine aminotransferase, anaplastic lymphoma kinase, creatinine, blood glucose, plasma sodium, and plasma potassium levels were normal. Subarachnoid hemorrhage was suspected as the likely diagnosis. He was treated with supportive care, but continued to complain of symptoms he had at admission. On his second day in the hospital, he complained of severe headache, and his mental state abruptly became worse, with the onset of confusion and anisocoric pupils. His Glasgow coma score was 10/15. An emergency left-sided craniotomy was performed, with aspiration of an encapsulated mass containing white-yellowish pus (150 mL). The pathological diagnosis was a brain abscess. Immediately after surgery, the patient was treated with ceftriaxone (2 g every 24 h intravenously) and metronidazole (500 mg every 8 h intravenously). The day after surgery, the patient's mental status returned to nearly normal (Glasgow coma score of 13/15), and he no longer complained of headache. The weakness in his left extremities improved significantly. Microscopic observation of the Gram stained smear of the abscess sample showed pleomorphic gram-positive coryneform bacteria. After 48 h at 37°C, aerobic culture grew minute, translucent, nonpigmented colonies with a small zone of clear hemolysis on 5% sheep blood agar. On the basis of the hemolytic pattern, a negative catalase reaction, and other biochemical test criteria, the isolate was identified as *A. haemolyticum* [11]. The isolate was found to be susceptible to penicillin, ceftriaxone, gentamicin, clindamicin, doxycycline, and vancomycin, but resistant to trimethoprim-sulfamethoxazole and ciprofloxacin by disk diffusion method. From the seventh day post-surgery, the patient received penicillin G (24 mU intravenously, daily for 21 days). Four weeks

later, the patient was successfully discharged from the hospital with no subsequent complications.

A. haemolyticum is a catalase-negative, gram-positive, or gram-variable rod whose morphology is dependent on the growth media and conditions [11]. This species (formerly *Corynebacterium haemolyticum*) is an infrequent cause of pharyngitis in children and young adults. It is occasionally isolated from wound infections and abscesses and is found in patients with meningitis, pneumonia, pyothorax, and septicemia [7–13]. To our knowledge, after a review of the indexed literature, we consider this to be the second reported case in which *A. haemolyticum* is documented as the etiological agent of a brain abscess (previously, 1 case in a child was reported) [10] and the first in an adult patient. Although *A. haemolyticum* is susceptible (thus far, universally) to penicillin by in vitro MIC testing, treatment failure despite adequate doses of phenoxymethylpenicillin has been documented [11, 13–15]. Most studies have found that *A. haemolyticum* is susceptible to all antimicrobials tested, except trimethoprim-sulfamethoxazole [11, 13–16]. In the current case, the isolate was also resistant to ciprofloxacin.

This case illustrates the aggressive and serious nature of systemic odontogenic infections in which resistant strains could be producing severe neurological complications. The careful identification of *Arcanobacterium* species and its corresponding antimicrobial susceptibility test is important, so a complete understanding of the role of these organisms in disease and proper management can be realized [17]. As was seen in our case, *A. haemolyticum* can be resistant to additional drugs other than trimethoprim-sulfamethoxazole (ciprofloxacin, in this report) and can cause severe life-threatening diseases.

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Coagulase-Negative Staphylococci in Diabetic Foot Osteomyelitis

TO THE EDITOR—In their study on the diagnostic value of swab cultures, compared with percutaneous bone biopsy specimen cultures, for patients with diabetic foot osteomyelitis, Senneville et al. [1] found coagulase-negative staphylococci much more frequently in bone specimens than in swab samples (25.6% vs. 4.6%; $P < .001$). As outlined in the accompanying editorial, this finding was rather unexpected, because coagulase-negative staphylococci are microorganisms with little suspected virulence [2]. If confirmed, these data may have an impact on the choice of antimicrobial regimen used in these patients, because coagulase-negative staphylococci are usually considered to be contaminants in such conditions.

According to the authors, “the finding of a higher proportion of coagulase-negative staphylococci isolates in bone biopsy samples, compared with swab samples, was independent of the findings of their microbiological laboratory, which identified all of the organisms cultured from both bone and swab samples (including bacteria from the skin flora) in accordance with the protocol they established in 1996 in their diabetic foot clinic” [1, p. 61]. However, in the article they refer to [3],

in which Senneville and colleagues discussed similar patients with the same procedures, although they observed similar discrepancies (in 31 patients with both swab and bone biopsy specimen cultures, coagulase-negative staphylococci were never cultured from swabs, despite that they were found in 8 bone biopsies; $P < .01$), Senneville and colleagues’ interpretation of this finding was much different: “this was likely to be related to the non-report of coagulase-negative staphylococci from superficial samples by our laboratory” [3, p. 929]. Could the authors clarify what made them change their interpretation between the 2 studies?

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Reply to Tattevin et al.

TO THE EDITOR—As noted by Tattevin et al. [1], in the 17 patients (not “31 patients,” as they wrote) with 20 episodes of diabetic foot osteomyelitis reported in 2001 by us and our colleagues [2], coagu-

lase-negative staphylococci strains accounted for 29.7% of the cases, and, in the present series [3], coagulase-negative staphylococci strains accounted for 25.6% of cases. This finding indicates that our results remained remarkably constant throughout the 1996–2004 period. It is true that we initially attributed the absence of coagulase-negative staphylococci strains in swab culture specimens to hypothetical nonreporting by the microbiology laboratory, but we must admit that we were not fully satisfied with this hypothesis and had further discussions with our laboratory staff to make sure that coagulase-negative staphylococci were not under-reported, which, indeed, proved to be the case. Therefore, as indicated in our article [3], all the coagulase-negative staphylococci strains yielded by both swab and bone cultures were, in fact, reported by our laboratory, in accordance with the protocol established in 1996 [2]. The surprisingly small proportion of coagulase-negative staphylococci strains cultured from our patients' samples (from 5 [5.6%] of 109 samples)—which, compared with the proportion cultured from bone samples, was a significant difference ($P < .001$)—has also been found by others; for instance, in the recent study by Ge et al. [4], *Staphylococcus epidermidis* was isolated from 111 (6.1%) of 1817 superficial specimens of chronic foot wounds obtained from comparable patients.

In their letter, Tattevin and colleagues also raise the question of whether coagulase-negative staphylococci might be responsible for osteomyelitis complicating chronic foot wounds in diabetic patients. This important question has been under discussion for years; but, at the time of writing this letter, no definite answer has been found. In a review of the current literature, Lipsky [5] already noted in 1997 that microorganisms such as *S. epidermidis* and *Corynebacterium* species, which are often considered to be contaminants, have been well documented as pathogens in cases of diabetic foot osteomyelitis. In some studies, up to 50% of deep-bone

cultures yielded coagulase-negative staphylococci [6–9]. However, Lipsky also stressed that “it is critical that the specimens for culture be obtained with proper precautions to avoid contamination” [5, p. 1321]. As indicated in our article [3], all the consecutive patients studied underwent surgical percutaneous bone biopsies, which were only performed by only trained senior orthopedic surgeons in the operating room under surgical aseptic conditions of sampling [3]. We believe that all possible precautions feasible in daily practice were taken to avoid contamination of the bone specimens obtained from our patients.

Unlike Tattevin and colleagues, we are not convinced that, if the coagulase-negative staphylococci strains in bone cultures were considered to be true pathogens, this would have an impact on the choice of antimicrobial regimen. In the present study [3], it would only have led to a change in the antibiotic treatment of 3 of the 10 and 5 of the 17 patients with polymicrobial and monomicrobial bone cultures, respectively, for whom a comparison with swab cultures was feasible.

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Efficacy of Short-Course Intramuscular Pentamidine Isethionate Treatment on Old World Localized Cutaneous Leishmaniasis in 2 Patients

TO THE EDITOR—Old world localized cutaneous leishmaniasis (LCL) is a protozoan skin infection that may be imported by travelers to Western countries [1, 2]. The treatment of Old World LCL still remains a real challenge, given the lack of efficacy of oral fluconazole and antimonials (administered either intramuscularly or intrasessionally) and the limitations of local treatments, such as “boiling the boil” [3]. The efficacy of intramuscular pentamidine isethionate (PI) has been demonstrated for New World LCL due to *Leishmania panamensis* [4] and *Leishmania guyanensis* [1, 5]. Therefore, PI may be an alternative for the treatment of Old World LCL. Here, we report 2 cases of Old World LCL that were resistant to first-line treatment and were successfully treated with PI.

Patient 1 was a 19-year-old man who returned from Mali (in west Africa) in December 2004. He presented with a 9-

month history of multiple cutaneous lesions, 1 ulcer on the left arm that was associated with nodular lymphangitis, and a nodule on the right elbow. Seven months earlier, he had been treated ineffectively in Mali with intramuscular injections of meglumine antimoniate. At admission, direct examination of a Giemsa-stained skin swab specimen revealed *Leishmania* species. The patient was assumed to be infected with *Leishmania major*, given the geographical location where he acquired LCL. A 6-week course of oral fluconazole (200 mg daily) failed to cure the patient clinically and parasitologically. Intramuscular PI (a 3-mg/kg dose given initially and then once again 2 days later) was administered during hospitalization. The treatment was well tolerated. Three months later, both the nodular and the ulcerative skin lesions had been cured, with hyperpigmented scar remaining, and the nodular lymphangitis had disappeared.

Patient 2 was a 50-year-old French woman who traveled to Egypt in January 2005 and who presented in September 2005 with a 6-month history of multiple skin lesions. Two months before her admission, she had received a diagnosis of LCL and had received a 6-week course of treatment with oral fluconazole (200 mg daily) without clinical success. Indeed, at admission, there were 3 papulonodular skin lesions on her face, 1 ulcer on her right elbow, and 2 maculopapular erythematous lesions each on her left knee and right forearm. Direct examination of a Giemsa-stained skin swab specimen confirmed the presence of *Leishmania* species. The patient was assumed to be infected with *L. major*, given the geographical location where she acquired LCL. Intramuscular PI (a 4-mg/kg dose given initially and then once again 2 days later) was administered during hospitalization. The treatment was well tolerated. Two months later, all of the cutaneous lesions had disappeared, some of which had left scars.

These 2 cases, in which first-line treatment with intramuscular antimonials or

fluconazole failed, suggest that short-course treatment with intramuscular injections of PI may be as effective for Old World LCL as it is for some forms of New World LCL. Indeed, in Colombia, treatment with 4 injections of PI (3 mg/kg given every other day) yielded a 96% cure rate in an area where *L. panamensis* predominates [4]. Pentamidine is also considered to be the first-line treatment in French Guyana, where 2 injections of PI (4 mg/kg of pentamidine base every other day) yielded a 95% cure rate in 205 patients infected with *L. guyanensis* [6]. In an open-label study of 11 cases of imported LCL, three 4-mg/kg intramuscular injections of pentamidine base given every other day yielded a success rate of 73% with good tolerance [7].

According to our results, and because the use of pentamidine salts is limited by their toxicity (which is sometimes dose dependent), we recommend administering 2 intramuscular injections of 3 mg/kg PI on days 0 and 2 of treatment for LCL therapy. Additional investigations are needed to assess the effectiveness, safety, and modalities (e.g., daily dose and number of intramuscular injections) of PI for the treatment of Old World LCL.

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What Can We Learn from Studies Comparing Linezolid with Vancomycin in Neutropenic Patients When Vancomycin Dosages Are Not Optimized?

TO THE EDITOR—Jaksic et al. [1] compared the safety and efficacy of linezolid (600 mg every 12 h), and vancomycin (1 g every 12 h) in febrile neutropenic patients. Although the authors specified that coinvestigators were allowed to monitor vancomycin levels in serum, in accordance with local practice, the article does not indicate whether adjustment of the vancomycin dosage could be performed throughout the study. The usual recommended intravenous dose of vancomycin is 30 mg/kg/day in adults; use of this dosage achieves serum concentrations of 25 mg/L (peak level) and 2 mg/L (trough level) in healthy volunteers [2], but pharmacokinetic studies of vancomycin therapy in neutropenic patients have shown a 3-fold increase of the initial volume of distribution and a shortened (3-fold) half-life, compared with values in healthy subjects [3, 4]. Although there have never been any definitive data correlating vancomycin efficacy and concentration, most experts will aim to achieve trough serum concentrations of ≥ 15 mg/L in patients with potentially severe infections [5], as

recommended by the American Thoracic Society–Infectious Diseases Society of America guidelines for the treatment of methicillin-resistant *Staphylococcus aureus* pneumonia [6]. The pharmacodynamic parameters that best express vancomycin bactericidal activity are the time during which serum concentration is greater than the MIC for the organism [2] and the area under the curve divided by the MIC [7]. In neutropenic patients, pharmacodynamic principles suggest that an optimal regimen of a time-dependent killing agent with little postantibiotic effect, such as vancomycin, should achieve serum concentrations greater than the MIC 100% of the time. This may be easily obtained with therapeutic drug monitoring or when vancomycin dosages are adapted to the patient's weight (i.e., 30 mg/kg/day) [8]. On the other hand, with the fixed dosages of vancomycin used in the study by Jaksic et al. [1] (1 g every 12 h), many patients may not achieve this pharmacodynamic parameter. Could the authors detail the range of vancomycin trough serum concentrations obtained in the health care centers where vancomycin serum levels were monitored?

In addition, given that the duration of neutropenia is an acknowledged risk factor for infectious complications [9], the delayed absolute neutrophil count recovery in patients receiving linezolid is of concern, despite the authors' assumption that "it may be attributable to physiological processes during recovery from acute bacterial infection" [1, p. 605]. Indeed, these physiological processes would not explain why neutrophil count recovery was significantly delayed in patients receiving linezolid, compared with those receiving vancomycin. Reports of linezolid myelotoxicity could be a serious limitation to the use of this agent in neutropenic patients [10].

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Reply to Tattevin and Camus

TO THE EDITOR—In the letter by Tattevin and Camus [1], 2 interesting points were

raised. The first concerns optimization of the vancomycin dosage. Although optimization of the vancomycin dosage may improve the efficacy of treatment, our study was not designed to address this question; rather, the study was designed to compare the 2 investigated medications in the usually recommended and prescribed doses for febrile, neutropenic patients with cancer, who can present with infections of varying sites and etiologies. For this reason, prespecified pharmacokinetic parameters were not defined, and systematic measurements of the vancomycin serum concentrations were not set by the protocol. The protocol directed sites to have 1 unblinded coinvestigator verify vancomycin serum concentrations and to adjust the dose, if necessary, in accordance with local practice guidelines. Because the study was not intended to look at dose optimization, sites were not required to send in concentration data. Therefore, we cannot address the pharmacokinetic/pharmacodynamic relationship with respect to vancomycin therapy, but we definitely can assess, in an unbiased way, the efficacy and tolerance of the drugs studied in their usually administered doses.

The second point concerns the delayed absolute neutrophil count recovery in certain subsets of patients who received linezolid. We were intrigued by the shorter time to defervescence and trends observed in prospectively defined hematologic events. Although the trends of hematologic events were not statistically significantly different in the overall patient population, we requested the post-hoc analysis that led to discovery that delayed neutrophil recovery was limited to the subset(s) of patients with good response to antimicrobial treatment, as shown by shorter time to defervescence. In contrast, there was no difference in time to defervescence in the fever of unknown origin (FUO) subset; the FUO subset also had no difference in time to neutrophil recovery (as shown in figure 2 of our study). This finding sheds a different light on the concern

expressed by Tattevin and Camus [1] and in some other (anecdotal) reports. This paradoxical finding was the basis for the hypothesis that delayed neutrophil recovery was not directly related to linezolid use. If linezolid itself had caused delayed neutrophil recovery, this should definitely have also been the case in the 183 patients with FUO (89 of whom were randomized to receive linezolid and 94 of whom were randomized to receive vancomycin). As presented in the article [2], in the FUO patient subset, no difference was detected in neutrophil recovery between linezolid recipients and vancomycin recipients, and this finding was paralleled by a lack of difference in the time to defervescence. Therefore, we were puzzled by the fact that, among patients with better response to linezolid (in the modified intent-to-treat and microbiologically evaluable subset), we found some trend of transient delay in neutrophil recovery. This led us to speculate about possible reasons for this observation. One explanation to this phenomenon could be an enhanced attraction of the neutrophil to the site of infection, thus causing a shift in the neutrophil kinetics. We believe that this observed phenomenon is interesting and warrants further study.

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