Correspondence

Assessing Risk Factors for Acquiring Antimicrobial-Resistant Pathogens: A Time for a Comparative Approach

Sir—We read with interest the article of Paramythiotou et al. [1], in which risk factors for acquiring multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) were assessed in case patients in an intensive care unit (ICU) by use of a sample of control patients who were presumably not colonized or infected with *P. aeruginosa.* Harris et al. [2] postulated that the optimal control group is one that represents the same source population from which the case patients are enrolled. The implications of the traditional selection of control patients from the population of patients with antibiotic-susceptible organisms has been brilliantly and extensively discussed elsewhere [2–5].

However, this study design has an important bias that was not recognized by Harris et al. [2] or Paramythiotou et al. [1], who adopted the same methodology in their study. When comparing patients from whom a resistant organism has been isolated with patients from whom such an organism has not been isolated, we cannot determine whether the variable is a risk factor for the resistant pathogen or only a risk factor for the pathogen independent of its susceptibility pattern. Thus, it seems that any conclusions that are based solely on studies with this design should be questioned.

This bias becomes clear when we analyze these studies. Paramythiotou et al. [1] reported that the duration of ciprofloxacin therapy was significantly longer among patients with MDRPA than among patients without *P. aeruginosa* and concluded that it is a risk for the acquisition of MDRPA. But was it really a risk factor for MDRPA, or was it a risk factor for *P. aeruginosa* only? These questions were not answered because this study design was not able to answer them.

It seems reasonable that a comparison of these findings with those of a study in which the same case patients were compared with control patients with *P. aeruginosa* that lacked the multidrug-resistance profile could help us better define real risk factors for MDRPA. It is to be expected that, if the duration of ciprofloxacin therapy is a risk factor for MDRPA, the duration will be distinct (i.e., longer), compared with that for a population with *P. aeruginosa* (not multidrug resistant) isolated. On the other hand, if such variable is a risk factor for *P. aeruginosa* only, it is expected that such difference will not appear when comparing the population with MDRPA with the population with *P. aeruginosa* (not multidrug resistant) isolated. Thus, we are able to infer with increased reliability whether the variable is a risk factor for MDRPA.

Previous studies apparently show the same bias [4, 6, 7]. In a study performed to illustrate the importance of control group selection on the results of risk factor analyses, Harris et al. [4] performed studies with distinct control groups using the examples of imipenem-resistant *P. aeruginosa* (IRPA), vancomycin-resistant enterococci, and ampicillin-sulbactam–resistant *Escherichia coli* [4]. In the IRPA study, patients with imipenem-susceptible *P. aeruginosa* (ISPA) comprised the control group in study A, and patients randomly selected from the same population comprised the control group in study B. Harris et al. [4] analyzed the impact on the ORs in a comparison of case patients with subjects in the distinct control groups. However, there was no qualitative analysis of the results when comparing them. In study B, Harris et al. [4] reported the length of hospital stay (i.e., time at risk) and the length of ICU stay as risk factors for the isolation of IRPA. The lengths of hospital stay and ICU stay are well-known risk factors for *P. aeruginosa* colonization [8]. Moreover, in study A, which compared patients that had IRPA with patients that had ISPA, there was no difference between both groups with respect to time at risk and length of ICU stay, suggesting that both, in fact, were risk factors for *P. aeruginosa* isolation. Similar results were reported in another study by Harris et al. [6], and other studies [7] have being performed with the same design, without a comparative analysis of a second study involving a control group comprised of patients with the susceptible pathogen and, consequently, with doubtful conclusions.

Paterson [5] has wisely stated that Harris et al. [2, 4, 6] have been leaders in the refinement of criteria for selecting control groups in studies on the risk factors associated with acquisition of antibiotic-resistant organisms. However, the search for an optimal design for such studies has not yet finished. A comparative approach in studies with distinct control groups allows us to make better conclusions about the risks of acquiring antibiotic-resistant organisms. This approach should be the next step in the refinement of study designs that analyzes risk factors for acquisition of antibiotic-resistant pathogens.

Acknowledgment

Conflict of interest. A.P.Z.: No conflict.

Alexandre Prehn Zavascki

Infectious Diseases Unit, Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre-RS, Brazil

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Reprints or correspondence: Dr. Alexandre Prehn Zavascki, Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, Serviço de Infectologia, 6690 Ipiranga Ave., 90610-000, Porto Alegre-RS, Brazil (alexandrepz@yahoo.com).

Clinical Infectious Diseases 2004; 39:871–2

Reply to Zavascki

Sir—We appreciate the comments from Zavascki [1] regarding control group selection in case-control studies of antibiotic-resistant bacteria. We agree with Zavascki that, when choosing random control subjects alone and comparing such subjects with case patients from whom multidrug-resistant isolates, such as multidrug-resistant *Pseudomonas aeruginosa* (MDRPS), have been recovered, readers "cannot differentiate whether the variable is a risk factor for the resistant pathogen or only a risk factor for the pathogen independent of its susceptibility pattern" [1, p. 871] (i.e., the reader cannot differentiate risk factors for MDRPS from risk factors for susceptible *P. aeruginosa*).

However, we disagree with the study design suggested by Zavascki [1], namely, that MDRPS case patients should be compared with susceptible control patients. As is outlined elsewhere [2–5], such a study design introduces a selection bias that affects the identification of risk factors (e.g., antimicrobial agents) and the magnitude of their effects (ORs) in case-control studies of antibiotic resistance. In fact, the aim of Harris et al. [4] was not to identify risk factors for the multidrug-resistant organisms but to demonstrate with real data what effect the selection bias might have on the results of case-control studies of antibiotic resistance [4].

We believe that a potential solution is the case-case-control study design that has been used in other studies [6–11]. In fact, the study by Harris et al. [7], in which risk factors for imipenem-resistant *P. aeruginosa* are assessed, uses the case-case-control study design and, thus, is not "performed with the same design," as suggested by Zavascki [1, p. 871].

The case-case-control study design uses 2 separate case-control analyses within a single study. The first group of cases is defined as patients with the resistant organism (e.g., MDRPS). The second group of cases is defined as patients with the susceptible organism (e.g., *P. aeruginosa*). The control subjects in each study are then randomly selected from the base population or the base cohort of interest. Two separate case-control analyses are performed within the single study. By comparing and contrasting the 2 analyses, risk factors specifically associated with isolation of the resistant organism can be identified without introducing a potential selection bias. We agree with Zavascki [1] that the search for an optimal design for antibiotic-resistance studies may not yet be completed, but we believe that comparing antibiotic-resistant case patients with antibiotic-susceptible control subjects is not the solution.

Acknowledgments

Conflict of interest. Y.C. has received grants, honoraria, travel support, and other forms of financial support from Bayer, Merck, Neopharm, Pfizer, Teva, and XTL Pharmaceuticals; A.D.H. has received a grant from Pfizer and is a consultant for Ortho-McNeil; and K.S.K. has received grants from Wyeth and Bayer, is a consultant for Bayer, and is on the speakers' bureaus of Bayer and Pfizer.

Anthony D. Harris,[1,2] Keith S. Kaye,[3] and Yehuda Carmeli[4]

[1]Veterans Affairs Maryland Healthcare System and [2]Department of Epidemiology and Preventive Medicine, University of Maryland, Baltimore; [3]Department of Medicine, Duke University Medical Center, Durham, North Carolina; and [4]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

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Reprints or correspondence: Dr. Anthony Harris, Dept. of Epidemiology and Preventive Medicine, University of Maryland, 100 N. Greene St. Lower Level, Baltimore, MD 21201 (aharris@epi.umaryland.edu).

Clinical Infectious Diseases 2004; 39:872–3

Laboratory Diagnosis of Urinary Tract Infections in Adult Patients

Sir—Several points regarding the laboratory diagnosis of urinary tract infection (UTI) deserve clarification to supplement the timely article by Wilson and Gaido [1]. First, it is imperative that physicians appreciate the distinction between microbiologically versus clinically significant bacteriuria. Although interpretive criteria based on specimen type, colony count, and number of organisms, such as the criteria shown in table 4 of the article by Wilson and Gaido [1], can be used to assess the likelihood that a positive urine culture result represents contamination instead of true bacteriuria, the mere presence of true (i.e., microbiologically significant) bacteriuria provides no information whatsoever regarding whether treatment is needed. This is a clinical judgment that is based on the recognition that, for adults, antimicrobial therapy for UTI should be reserved almost exclusively for treating symptomatic infections. Asymptomatic bacteriuria is usually clinically insignificant and should be treated only in pregnant women and before invasive urologic procedures, regardless of the bacterial colony count, organism, and degree of associated pyuria.

Second, several studies have shown that, in young women with acute dysuria, so-called low-count bacteriuria is usually both microbiologically and clinically significant and is substantially prevalent, such that a concentration criterion of $\geqslant 10^5$ cfu/mL (or even $\geqslant 10^4$ cfu/mL) for clinical significance is highly insensitive. Use of the term "urethral syndrome" to describe the disorder present in dysuric women with low-count coliform bacteriuria may be more misleading than helpful, because most of these patients actually have straightforward *Escherichia coli* UTI that will respond to standard single-dose or 3-day treatment with an appropriate agent.

Third, among chronically catheterized patients, high-count (and often polymicrobial) bacteriuria is almost universally prevalent. Although these organisms might be considered to be contaminants in the sense that they are contaminating the catheter system, they represent true bacteriuria and cannot be dismissed as microbiologically or clinically irrelevant if the patient has symptoms possibly attributable to UTI. Thus, when clinical suspicion for symptomatic UTI is high in such patients, physicians must ask the laboratory to evaluate the multiple organisms involved to facilitate effective antimicrobial therapy, particularly because the specific organisms that are present, as well as the associated antibiograms, are highly unpredictable in these cases.

Acknowledgment

Conflict of interest. J.R.J. has received grants and/or honoraria from Merck, Bayer, Ortho-McNeil, Wyeth-Ayerst, Fujisawa, and Rochester Medical.

James R. Johnson
Infectious Diseases Section,
Veterans Affairs Medical Center,
Minneapolis, Minnesota

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Reprints or correspondence: Dr. James R. Johnson, Infectious Diseases Section (111F), VA Medical Center, 1 Veterans Dr., Minneapolis, MN 55417 (johns007@umn.edu).

Clinical Infectious Diseases 2004; 39:873

Reply to Johnson

Sir—We thank Dr. Johnson [1] for his letter regarding our recent article [2]. We agree with his first comment regarding the distinction between microbiologically versus clinically significant bacteriuria. The interpretation of urine culture results can be challenging, both for the clinical microbiologist and for the clinician. Microbiological criteria for the determination of contamination versus true bacteriuria are useful in guiding the work up of cultures, but as Dr. Johnson [1] points out, the decision whether to treat is ultimately based on clinical judgment. This is analogous to the use of case definitions for epidemiological analysis; although a suspected case warrants further epidemiological and/or clinical evaluation, a case definition alone may not be sufficient to initiate or guide therapy. In the same way, microbiological and clinical definitions and interpretations serve different purposes.

With respect to Dr. Johnson's second point, we agree that a definition of $\geqslant 10^5$ cfu/mL or $\geqslant 10^4$ cfu/mL is insensitive for some patients with urinary tract infections (UTIs). Unfortunately, microbiologists must make arbitrary decisions on the basis of available data as to what cutoff value to use. For a number of reasons, most laboratories use a higher cutoff value, even while acknowledging the issue raised by Dr. Johnson.

We are in strong agreement with Dr. Johnson's third point: just as clinicians cannot interpret results of microbiological analysis without integrating the patients' clinical signs and symptoms, microbiologists cannot work up cultures appropriately without basic information about the specimen type and the date and time of collection, as well as other pertinent clinical information. Effective communication between clinician and laboratorian is

the first step in providing meaningful microbiological data and, ultimately, good patient care.

Saying that the diagnosis of UTI requires correlation of clinical presentation with laboratory results may summarize the unifying concept alluded to by Dr. Johnson [1] and expressed in our article [2]. The role of the laboratory is to provide accurate results of urine cultures, with quantification of bacterial growth and antimicrobial-susceptibility testing when applicable. To this effect, laboratorians use previously established criteria, however imperfect, to determine the extent of work up required for urine culture isolates. Ultimately, clinicians should determine the likelihood that UTI will require therapy on the basis of clinical and laboratory data.

Acknowledgment

Conflict of interest. M.L.W. and L.G.: No conflict.

Michael L. Wilson and Loretta Gaido

Department of Pathology and Laboratory Services, Denver Health Medical Center, and Department of Pathology, University of Colorado School of Medicine, Denver, Colorado

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Reprints or correspondence: Dr. Michael L. Wilson, Dept. of Pathology and Laboratory Services, Denver Health Medical Ctr., Mail Code #0224, 777 Bannock, Denver, CO 80204 (michael.wilson@dhha.org).

Clinical Infectious Diseases 2004; 39:873–4

No Evidence for the Effectiveness of ClO_2-Generating Gloves

Sir—In his recently published article, Barza [1, p. 861] claimed that ClO_2-generating gloves "are able to reduce counts of *S. aureus, L. monocytogenes, E. coli*, and *S.* Typhimurium *substantially and quickly* on the surface of the gloves" (emphasis ours). We regard this as a misleading claim that is based on insufficient experimental evidence and inappropriate statistical analysis. In fact, the small amount of experimental evidence presented by Barza [1] seems, rather, to indicate only a clinically insufficient reduction in bacterial counts, even after unrealistically long waiting times and the additional requirement of light exposure. Unfortunately, Barza's unjustified claim has already found its way into local newspapers, such as the *Hannoversche Allgemeine Zeitung* (Hannover, Germany) [2].

To substantiate our appraisal of Barza's claim, we refer the reader to the left-hand half of table 1 in his article [1], which gives log counts of bacteria for 2 control and 2 ClO_2-generating gloves after various waiting times. Apparently, results in the same column refer to counts obtained at different times but on the same glove, and therefore the results cannot be regarded as being statistically independent. This invalidates the use of the Wilcoxon signed rank test or any other comparable test for analysis of these data.

Any such statistical test could be legitimately applied to the observations at a single fixed waiting time (e.g., 1 min), but that would not lead to a statistically significant result because of the tiny sample size. Furthermore, the observed reductions in counts of ~3 logs, whether statistically significant or not, are clinically insufficient, because alcohol-based hand hygiene already yields a reduction in the count of 5 logs after 30 s [3].

We fear that Barza's suggestion could lead to very risky health care practices, because use of these special gloves can result in a false sense of security. Sufficient evidence for the use of alcohol-based hand rubs exists not only for laboratory outcomes, but also for clinical outcomes [4–6]. Therefore, the use of alcohol-based hand hygiene is the just recommendation [7].

Acknowledgment

Conflict of interest. All authors: No conflict.

Frauke Mattner,[1] Lutz Mattner,[2] and Iris F. Chaberny[1]

[1]Institute for Medical Microbiology and Hospital Epidemiology, Hannover, and [2]Institute of Mathematics, University of Luebeck, Luebeck, Germany

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Reprints or correspondence: Dr. Frauke Mattner, Medizinische Hochschule Hannover, Carl-Neuberg-Straβe 1, 30625 Hannover, Germany (mattner.frauke@mh-hannover.de).

Clinical Infectious Diseases 2004; 39:874

Reply to Mattner et al.

Sir—Hand hygiene in clinical and food-handling environments always should be approached using complementary practices that include thorough washing of hands, use of alcohol-based hand rubs, and wearing of single-use gloves. At no time should only one of these practices be used alone. The ClO_2-generating gloves described in my earlier article [1] could augment currently recommended practices and should provide additional pro-

tection in situations in which users are not fully adherent to these recommendations. The gloves are not intended to replace standard hand hygiene but, rather, to supplement it.

Mattner et al. [2] are mistaken in inferring that the measurements over time given in table 1 (and in the other tables) were successive measurements of the same glove. As stated in the table notes, each measurement is the result for a single glove; no glove is represented more than once in the data. Accordingly, the Wilcoxon signed rank test was appropriate for statistical analysis.

The determination of the "sufficiency" of the magnitude and rapidity of the effect of these gloves must be related to the environment of use. The experiments reported demonstrate the ability of the gloves to rapidly (i.e., within 2 min of donning) and significantly reduce high levels of contamination. That the technology is triggered by light is part of its beauty: the ClO_2 will be dissipated not while the gloves lie in the box but only when they are worn.

Acknowledgment

Conflict of interest. M.B. is a shareholder and member of the Board of Directors of Bernàrd Technologies, which oversaw the manufacturing of the ClO_2-generating gloves under discussion.

Michael Barza

Department of Medicine, Carney Caritas Hospital, Boston, Massachusetts

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Reprints or correspondence: Dr. Michael Barza, Dept. of Medicine, Carney Caritas Hospital, 2100 Dorchester Ave., Boston, MA 02124 (mbarza@cchcs.org).

Clinical Infectious Diseases 2004; 39:874–5

Outbreak of *Clostridium difficile* Infection and Gatifloxacin Use in a Long-Term Care Facility

SIR—We read with interest the report by Gaynes et al. [1] describing a gatifloxacin-associated "epidemic" of *Clostridium difficile*–associated diarrhea (CDAD) in the Atlanta, Georgia Veterans Affairs Medical Center Long-term Care Facility (LTCF). The report by Gaynes et al. [1] reminds the reader that CDAD is associated with several different antibiotics, not the least of which are the fluoroquinolones [2, 3]. However, to suggest that there is a higher incidence of CDAD with gatifloxacin therapy than with levofloxacin, on the basis of a retrospective analysis, is a conclusion made with greater confounding variables than supporting evidence. In addition, these findings are not consistent with previously published reports demonstrating the association of levofloxacin therapy with increasing incidences of CDAD [4, 5]. In fact, a recent analysis of cases of *C. difficile* infection at our institution found a statistically significant increase in the incidence of CDAD associated with the use of levofloxacin and third generation cephalosporins, but not other fluoroquinolones [6]. Replacement of levofloxacin in the formulary with ciprofloxacin and gatifloxacin in 2000 resulted in a significant decline in the observed rates of *C. difficile* infection at our institution. Likewise, Changela et al. [7] conducted a cohort-controlled study to review the risk factors associated with CDAD at a Veterans Affairs medical center in Illinois, and they found antibiotic use to be significantly associated with *C. difficile* infection, with levofloxacin use being significantly with CDAD, compared with the cohort-control group. This is not to suggest that levofloxacin is the sole culprit causing CDAD; there are reports of CDAD that identify moxifloxacin use and ciprofloxacin use as causes, as well [8, 9].

We do know from the study of Gaynes et al. [1] that a "generalized cleaning of the LTCF was performed with a hypochlorite disinfectant during the period of 9–12 June 2002" just before switching the unit back to levofloxacin. Perhaps the decline in the rate of *C. difficile* infection was directly related to the sterilization of the LTCF and other infection control procedures implemented, rather than to the switch in antimicrobial therapy. To do a reasonable comparison between the fluoroquinolone "study periods," the authors should have included a case-control study during the levofloxacin dosing period, as well, and a thorough review of all concomitant antibiotics each patient received during each study period. It also appears that the rate of *C. difficile* infection in the acute-care facility was increasing (there were no data before January 2001) and the rate of CDAD associated with gatifloxacin use in the LTCF was actually lower than the rate with levofloxacin reported in the acute-care facility at the same time (~1.3 vs. ~1.9 cases per 1000 patient-days, respectively). Because these patients were likely being transferred to and from the acute-care facility—certainly the LTCF patients shared diagnostic facilities with patients in the acute-care facility—the problem with *C. difficile* may have existed in the hospital and been spread to the LTCF, or vice versa. It would be important to note whether there was a trend in the incidence of CDAD at the both sites prior to January 2001 to determine whether it was indeed increasing?

Lastly, Gaynes et al. [1] do report that 25 (55%) of 45 of the isolates from the acute care facility and 2 (50%) of 4 of the isolates from the LTCF were the same type and were all resistant to fluoroquinolones. Does this finding imply that this indeed was an outbreak of a single strain? What methods were utilized to determine that all strains with identical susceptibility patterns were indeed all type A? Perhaps a more in-depth molecular analysis would have addressed many of the questions regarding the source of the strains and how infection-control and sterilization proce-

dures may have contributed to the problems seen at this institution.

Acknowledgment

Conflict of interest. J.M.: No conflict.

John Mohr

University of Texas Health Science Center Houston, Department of Internal Medicine/Division of Infectious Diseases, Houston, Texas

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Reprints or correspondence: Dr. John Mohr, University of Texas Health Science Center Houston, Department of Internal Medicine/Division of Infectious Diseases, 6431 Fannin, JFB 1.728, Houston, TX (john.mohr@uth.tmc.edu).

Clinical Infectious Diseases 2004; 39:875–6

Reply to Mohr

Sir—We thank Dr. Mohr [1] for his comments but believe that he has misunderstood our argument. We purport to explain the rise in the rate of *Clostridium difficille*–associated diarrhea (CDAD) in light of a change to gatifloxacin therapy for patients in this LTCF [2]. We agree that clindamycin exposure is also a strong risk factor for CDAD; indeed, 5 patients had clindamycin exposure that appeared to account for their CDAD. The 2 antibiotics gatifloxacin and clindamycin accounted for CDAD in 19 of 21 patients in the case-control study. The other two patients were exposed to other antibiotics.

Dr. Mohr's assertion that replacement of levofloxacin on the formulary with ciprofloxacin and gatifloxacin in 2000 resulted in a significant decline in observed rates of *Clostridium difficile* infection at his institution, is unreferenced. This report would add to the literature if additional details regarding patients, risk factors, and other information are provided.

That other authors found associations between CDAD and use of other antibiotics, including fluoroquinolones, is not surprising [3, 4]. The pathogenesis of CDAD, which involves alterations in gastrointestinal tract flora and possibly intrinsic or acquired resistance to the antimicrobial agent, as suggested by Dr. Gerding [5], is indeed complex. Risk factors at each institution may differ.

Although a generalized cleaning of the LTCF with a hypochlorite disinfectant occurred just before therapy for patients on the unit was switched back to levofloxacin, we believe that a single effort at disinfection would not result in a sustained reduction in the rate of CDAD and would not account for the change in rates observed at the acute-care facility.

Dr. Mohr also states, "To do a reasonable comparison between the fluoroquinolone 'study periods,' the authors should have included a case-control study during the levofloxacin dosing period" [1, p. 875]. We considered such a case-control study at the time but concluded that that study would have been confounded by the use of historical controls, such as the proximity to case patients (who in some instances were a roommate or present in an adjacent room).

We are unsure of the relevance of the comparison between the number of cases per 1000 days for the acute and long-term care facilities, as severity of illness and antibiotic exposure differed markedly. With respect to changes in the CDAD rates at the acute-care facility, we stated in the legend to figure 2 [2] that the rate of CDAD at the acute-care facility differed significantly ($P < .002$) for either period of levofloxacin use when compared with the period of gatifloxacin use. We agree that CDAD may have been spread from the LTCF to the acute-care facility, or vice versa; indeed, the improvement of CDAD rates after therapy was switched back to levofloxacin in the LTCF may have helped the eventual improvement at the acute-care facility, but this explanation seems less likely because there was a 4-month difference in the time of the switch back to levofloxacin between the LTCF and the acute care facility. Whether there was an increase in CDAD rates before January 2001 is unknown and does not seem to affect the results presented.

Lastly, Dr. Mohr addresses the possibility that a clonal strain was responsible for causing the outbreak. We are unsure of his point. If he is suggesting that the outbreak was caused by an unusually virulent strain that happened to enter the facility at the time of gatifloxacin use and accounted for an increased rate of CDAD, independently of the antibiotic change, then we believe it is equally likely that, when the environment was rendered suitable for *C. difficile* to thrive, one strain would be more competitive than the others and would rise to the top. The method used for determining types is clearly stated in the article.

Acknowledgment

Conflict of interest. All authors: No conflict.

Robert Gaynes, David Rimland, Edna Killum, H. Ken Lowery, Ted Johnson, George Killgore, and Fred C. Tenover

Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

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Reprints or correspondence: Dr. Robert Gaynes, Div. of Healthcare Quality Promotion, CDC, MS E-55, 1600 Clifton Rd., Atlanta, GA 30333 (Rpg1@cdc.gov).

Clinical Infectious Diseases 2004; 39:876–7

Antimicrobial Mechanisms of Cranberry Juice

Sir—In their treatment of the potential antimicrobial mechanisms of cranberry juice, Raz and colleagues [1] emphasize its antiadherent activities and discount its significant role in urinary acidification. We would like to highlight a third potential mechanism: the *nonenzymatic* generation of nitric oxide (NO). Nitric oxide possesses potent antimicrobial activities that are both time- and concentration-dependent. Enzymatically, NO can be generated from L-arginine and molecular oxygen by NO synthases; however, NO can also be generated in vivo nonenzymatically by dismutation of nitrite to NO and NO_2 under mildly acidic conditions [2, 3]. In urinary tract infections, acidified nitrite may be a physiologically relevant source of NO produced by bacterial nitrate reductase activity and/or the local induction of inflammation-driven NO synthase activity.

Carlsson and colleagues [1] demonstrated that mild acidification (pH range, 5.0–6.0) of urine containing levels of nitrite comparable to those observed in nitrite-positive urine specimens from patients with urinary tract infection released significant amounts of NO gas [2]. This release was potentiated by the presence of physiologically achievable levels of ascorbic acid. Under the latter conditions, growth of *Escherichia coli, Staphylococcus saprophyticus,* and *Pseudomonas aeruginosa* was significantly attenuated [4, 5]. Of note, the antibacterial effects observed with the addition of ascorbic acid were independent of urine pH. This finding agrees well with numerous prior observations that ascorbic acid is a poor acidifier of urine and supports the notion that the enhanced antibacterial effects of ascorbic acid are due to a reducing capacity that, in turn, facilitates nonenzymatic dismutation of acidified nitrite to NO.

It is plausible, therefore, that the antibacterial effects of cranberry juice may, in part, be explained by the total reducing capacity of its components, including ascorbic acid, which facilitates nonenzymatic generation of NO. Admittedly, the time- and concentration-dependent properties of the antibacterial effects of NO predict a limited role for such a mechanism in both prophylaxis and treatment; these limits are a consequence of variations of both pathogen-specific production of nitrite and the persistence of NO in the urinary tract. Nonetheless, careful evaluation of the *relative* role of such a mechanism may be important for defining the clinical efficacy of cranberry juice as a nonantibiotic alternative for the prophylaxis against urinary tract infections.

Kyu Y. Rhee and Macarthur Charles

Division of International Medicine and Infectious Diseases, Weill Medical College of Cornell University, New York, New York

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Reprints or correspondence: Dr. Kyu Y. Rhee, Weill Medical College, Cornell University, 1300 York Ave. A-421, New York, NY 10021 (kyr9001@nyp.org).

Clinical Infectious Diseases 2004; 39:877

Intracellular Pharmacology of Emtricitabine and Tenofovir

Sir—Anderson et al. [1] are commended for their scholarly review of the cellular pharmacology of nucleoside and nucleotide reverse-transcriptase inhibitors (NRTIs) and its relationship to observed toxicities. We wish to provide clarification of the cellular pharmacology data for emtricitabine and tenofovir.

The intracellular half-life in PBMCs for emtricitabine, noted in the review [1] as 20 h, is not accurately reflective of the results reported by Rousseau et al. [2], in which the emtricitabine triphosphate half-life was estimated to be >20 h. Moreover, an additional study involving healthy subjects who received a daily 200-mg dose of emtricitabine for 10 days reported an emtricitabine triphosphate half-life of 39 h [3]. This latter value is from more-rigorous pharmacokinetic analyses and provides a robust estimate of the intracellular half-life, because multiple samples were obtained over a 120-h period following receipt of the last dose of drug.

In addition, the intracellular half-life for tenofovir diphosphate, the active phos-

phorylated anabolite of tenofovir, was not fully elucidated in the review by Anderson et al. [1]. In vitro, tenofovir diphosphate has been shown to exhibit a half life of 10–50 h in stimulated and resting PBMCs [4], and clinical pharmacokinetic data from HIV-infected patients have been recently reported. The tenofovir diphosphate intracellular decay was evaluated for a period of >72 h following discontinuation of tenofovir therapy in 8 HIV-infected subjects receiving a triple-NRTI regimen [5]. The estimated tenofovir diphosphate intracellular half-life was ⩾60 h, and all 8 subjects had measurable intracellular concentrations during the 60–72-h sampling period.

Within the NRTI class, emtricitabine and tenofovir exhibit long and complimentary intracellular half-lives. This pharmacokinetic symmetry is desirable within the context of HAART. For example, results of the Stop study [6] showed that, consistent with a long plasma half-life, a significant period of efavirenz monotherapy may be undergone by patients following cessation of a HAART regimen. To address this issue, Taylor et al. [6] has reported that zidovudine and lamivudine may need to be continued for several days after stopping efavirenz to cover the so-called "nonnucleoside tail." As noted by Anderson et al. [1], these data suggest that pharmacokinetic characteristics of individual drugs should be considered when selecting agents for a HAART regimen, because it likely plays a significant role in various clinical situations, such as suboptimal adherence, unplanned treatment interruptions, and treatment discontinuations. In addition, from a practical standpoint, choosing antiretrovirals with similar intracellular kinetics will help clinicians and patients to avoid the complex dosing schedules that may be needed when using antiretroviral drugs with disparate pharmacokinetics.

In summary, continuing advances in the knowledge of intracellular pharmacology are enhancing our ability to best use NRTIs for the benefit of the patients.

Acknowledgment

Conflict of interest. All authors are employees and stockholders of Gilead Sciences.

Robert C. Stevens,[1] M. Robert Blum,[2] Franck S. Rousseau,[2] and Brian P. Kearney[1]

[1]Gilead Sciences, Foster City, California; and [2]Gilead Sciences, Durham, North Carolina

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Reprints or correspondence: Dr. Robert C. Stevens, Gilead Sciences, 333 Lakeside Dr., Foster City, CA 94404 (rstevens@gilead.com).

Clinical Infectious Diseases 2004; 39:877–8

Reply to Stevens et al.

Sir—We appreciate the update provided by Stevens et al. [1] on the intracellular half-life of tenofovir-diphosphate in HIV-infected patients. At the time of publication, this information was not available.

The discussion regarding emtricitibine-triphosphate raises some important points. First, most of the studies that report intracellular triphosphate concentrations of nucleoside and nucleotide analog reverse-transcriptase inhibitors (NRTIs) in HIV-infected patients are small and not rigorously designed to capture a full pharmacokinetic profile. This is true for emtricitibine-triphosphate, for which the half-life was estimated from a dose-escalation study designed to evaluate dose-proportional drug exposures and antiviral effects, not the half-life of the triphosphate [2]. This is also particularly true for dideoxyadenosine-triphosphate (active triphosphate for didanosine), for which the half-life value had to be estimated from a small data set that was not well suited for characterizing this information [3].

Second, the longer half-life for emtricitabine-triphosphate referenced by Stevens et al. [1] was generated in healthy volunteers [4]. Although the study [4] was rigorous for determining half-life, the pharmacologic values we listed in table 2 of our report [5] were specifically derived in HIV-infected patients. One of the premises of our review was that the presence and severity of HIV disease influences the intracellular pharmacology of NRTIs. We suggested that HIV-associated proinflammatory activity may cause stimulated cells to generate higher concentrations of NRTI-triphosphates in tissues that are sensitive to that proinflammatory stimulation. This may include PBMCs in which NRTI-triphosphates are quantified and also other tissues where toxicities actually occur. In the study by Wang et al. [4], emtricitibine-triphosphate was also measured in an HIV-infected cohort, and concentrations appear to be ~3-fold higher in this cohort, compared with the healthy volunteers. We believe it is important to understand the pharmacology of NRTIs both in HIV-infected and -uninfected per-

sons, because these agents are also used for postexposure prophylaxis.

Finally, Stevens et al. [1] gave an excellent illustration of the potential clinical utility of half-life data in the context of treatment interruption with regimens that include efavirenz or nevirapine. Because these agents have relatively long half-lives, they will linger, while antiretrovirals with shorter half-lives will disappear more rapidly. This may cause a period of virtual monotherapy, which may facilitate drug resistance, particularly for antiretrovirals with a low genetic-resistance barrier [6]. To prevent this scenario, the British HIV Association guidelines recommend switching efavirenz or nevirapine to a protease inhibitor for 1–2 weeks before stopping the regimen or continuing the NRTIs for 1 week after stopping efavirenz or nevirapine [7]. However, the guidelines do not discuss the relevance of NRTI-triphosphate half-lives. This may be an important consideration given the 7-h to ⩾60-h half-life range among the various NRTI-triphosphates [1, 3]. It should also be noted that stopping a regimen containing agents with longer NRTI-triphosphate half-lives and a protease inhibitor may require extending the protease inhibitor to avoid virtual NRTI monotherapy, which can also confer risk of high-level resistance with a single mutation in some cases [6].

In summary, we agree that the safest and most efficacious antiretroviral treatment strategies should include consideration of NRTI-triphosphate concentrations.

Acknowledgment

Conflict of interest. All authors: No conflict.

Peter L. Anderson,[1] Thomas N. Kakuda,[3] and Kenneth A. Lichtenstein[2]

[1]School of Pharmacy and [2]Department of Medicine, University of Colorado Health Sciences Center, Denver; and [3]Roche Laboratories, Nutley, New Jersey

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Reprints or correspondence: Dr. Peter L. Anderson, School of Pharmacy, Dept. of Clinical Pharmacy, University of Colorado Health Sciences Center, Box C238, 4200 E. 9th Ave., Denver, CO 80262 (peter.anderson@uchsc.edu).

Clinical Infectious Diseases 2004; 39:878–9

Use of the Echinocandins (Caspofungin) in the Treatment of Disseminated Coccidioidomycosis in a Renal Transplant Recipient

We report a case of disseminated coccidioidomycosis in a renal transplant recipient treated successfully with caspofungin. A 51-year-old man who received a cadaveric renal transplant was admitted with a 3–4 week history of fever, chills, dry cough, and weight loss of 10–12 lbs. His immunosuppressive therapy included Prograf, CellCept, and prednisone. Vital signs included a temperature of 103.2°F, blood pressure of 102/78 mm Hg, pulse of 98 beats/min, respiratory rate of 28 breaths/min, and oxygen saturation of 80%. Clinical examination revealed a moderately ill-appearing man in mild respiratory distress with expiratory rales and crackles in both lung fields. The rest of the examination was unremarkable. Diagnostic studies included a chest x-ray, which showed evidence of multiple nodules without any mediastinal masses. A CT scan confirmed findings from the chest x-ray. Significant laboratory values included the following: serum glutamic oxaloacetic transaminase (SGOT), 88 IU/L; serum glutamic pyruvic transaminase (SGPT), 92 IU/L; alkaline phosphatase, 210 IU/L; bilirubin, 1.2 mg/dL; WBC, 12.0/mm^3; hemoglobin, 9.6 g/dL; platelet count, 411 K/mm^3; and serum creatinine, 1.9 mg/dL. Serum cocci titers were undetectable. The patient underwent a bronchoscopy and biopsy of a nodule, which revealed the presence of abundant *Coccidioides immitis*. Initially, the patient was treated with fluconazole. However, within 3 days the level of serum creatinine increased to 3.2 mg/dL, and the levels of SGOT and SGPT increased to 126 IU/L and 137 IU/L, respectively. Fluconazole was then switched to liposomal amphotericin at 3mg/kg/day. The patient remained febrile. Levels of SGOT and SGPT increased to 234 IU/L and 354 IU/L, respectively. The level of serum creatinine increased to 4.2 mg/dL.

On day 7 of hospitalization, treatment with liposomal amphotericin B was switched to treatment with caspofungin. The patient was also treated with caspofungin (50 mg per day, iv) for a total of 4 weeks. Within the first 5 days after initiating therapy with caspofungin, the patient defervesced and started to feel better, with resolution of the respiratory distress, cough, and chills. His renal failure and abnormal liver function also began to improve over the next 2 weeks. Fever, shortness of breath, and cough had completely resolved when he was seen for followup 4 weeks later. He was subsequently treated

with fluconazole 200 mg per day for the next 6 months.

Followup during the next 6 months revealed normalization of renal insufficiency and liver function and showed reduction in the size and number of nodules visible on CT scan. His immunosuppressive therapy, although initially decreased at the time of acute infection, was increased to appropriate doses.

A CT scan performed 6 months later showed minimal residual nodules and scar tissue. The serum cocci levels, however, remained undetectable during this illness. Followup 1 year later revealed no recurrence of the coccidiomycosis, although he is still being treated with suppressive fluconazole.

This case has several interesting aspects. This appears to be the first case of a renal transplant recipient with coccidioidomycosis who has been treated successfully with caspofungin. The brief treatment with fluconazole and liposomal amphotericin was probably unlikely to have had sufficient activity against *C. immitis* to be effective as "real antifungals" in this case. There is some in vitro data on the activity of caspofungin in coccidioidomycosis [1–3]. The murine model of infection caused by *C. immitis* shows that caspofungin appears to be active, with the minimal effective concentration (MEC) being a better predicator of therapeutic outcome than the MIC. In this study [1], mice infected with 1 of 2 strains of *C. immitis*—each mouse having a MEC of 0.125 μg/mL, one having a MIC of 8 μg/mL, and the other having a MIC of 64 μg/L—responded equally well to treatment with caspofungin. The presence of multiple nodules in the lungs suggests this patient probably had severe coccidioidomycosis, which may be a reflection of infection prior to transplantation. The use of liposomal amphotericin in renal transplant patients with coccidioidomycosis could possibly result in progressive renal insufficiency and loss of the allograft; therefore, treatment with liposomal amphotericin may not always be useful. Alternative therapy with echinocandins may be an option in patients with coccidioidomycosis in whom azole therapy is contraindicated. Further studies evaluating this drug in nontransplant patients as well as transplant recipients is warranted.

Acknowledgment

Conflict of interest. S.A.: No conflict.

Suresh Antony

Department of Internal Medicine, Division of Infectious Diseases, Texas Tech University Health Sciences Center, El Paso, Texas

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Reprints or correspondence: Dept. of Internal Medicine, Div. of Infectious Diseases, Texas Tech University Health Sciences Center, 7848 Gateway E., El Paso, TX 79915 (santony@elp.rr.com).

Clinical Infectious Diseases 2004; 39:879–80
 1058-4838/2004/3906-0032$15.00