

Correspondence

Nucleoside Reverse-Transcriptase Inhibitor Use, Cirrhosis, and End-Stage Liver Disease in HIV-Infected Patients

TO THE EDITOR—Guaraldi et al. [1] recently reported that nonalcoholic fatty liver disease (NAFLD) was common among HIV-infected patients who had neither evidence of chronic viral hepatitis nor a history of significant alcohol use. In addition, cumulative nucleoside reverse-transcriptase inhibitor (NRTI) exposure was an independent risk factor for NAFLD. Contrary to their assertion that few people with NAFLD experienced progression to nonalcoholic steatohepatitis (NASH), we describe 2 patients who had virologically well-controlled HIV infection and without traditional risk factors for NASH, whose cases progressed to cirrhosis presumably related to prolonged NRTI exposure.

Case 1 occurred in a 47-year-old non-obese (body mass index [calculated as weight in kilograms divided by the square of height in meters], 20.5–27.8) white man. HIV infection had been diagnosed in 1995. His recent CD4 cell count and HIV load were 233 cells/ μ L and <50 copies/mL, respectively. It was noted that the patient experienced hepatitis in 2001, 5 years after he had initiated stavudine treatment. His antiretroviral therapy regimen was modified to include didanosine. The total duration of exposure to these NRTIs was 415 weeks. In 2005, the patient developed NASH, which progressed to cirrhosis; complications included bleeding esophageal varices, thrombocytopenia, and portal hypertension. A liver biopsy was performed in 2006, and examination of the specimen demonstrated steatohepatitis and periportal fibrosis.

Case 2 occurred in a 51-year-old non-

obese (body mass index, 20.0–22.5) white man. The patient received a diagnosis of HIV infection in 1988 and had a recent CD4 cell count of 221 cells/ μ L and HIV load of <50 copies/mL; he had received prolonged antiretroviral therapy with stavudine and didanosine (total duration of exposure to these NRTIs, 539 weeks). The patient developed NASH, which progressed to cirrhosis; sequelae included recurrent bleeding esophageal varices, thrombocytopenia, and portal hypertension with gastropathy, which necessitated a transjugular intrahepatic portosystemic shunt procedure. A liver biopsy performed in 2005 demonstrated significant cirrhosis consistent with drug toxicity.

Both patients had no history of chronic viral hepatitis, diabetes, dyslipidemia, obesity, or significant alcohol use, and both have since been evaluated for liver transplantation.

Although Guaraldi et al. [1] found no association between cumulative exposure to a single NRTI or commonly prescribed NRTI combinations (e.g., stavudine and didanosine) and NAFLD, others have reported a correlation between the use of dideoxynucleoside analogues (e.g., stavudine and didanosine) and the development of hepatosteatosis. However, several of these studies involved patients with hepatitis C virus coinfection [2–4]. Reportedly, the most notable drugs with a strong association with hepatosteatosis are those that have the strongest capacity to deplete mitochondrial DNA (i.e., zalcitabine, didanosine, and stavudine) through an interaction with DNA polymerase- γ , causing chronic mitochondrial toxicity [4–6].

Although, in the general population, NAFLD presumably has a low rate of progression to NASH and cirrhosis [7], it appears that there was an unusually rapid

progression in our patients, who had prolonged NRTI exposure. Guaraldi et al. [1] suggest that the prevalence of more-advanced liver disease may have been underestimated as a result of the lack of histologic confirmation of NAFLD and the limited ability of CT to discern between NAFLD and NASH. NAFLD represents another long-term toxicity related to antiretroviral therapy. It is likely that cases of end-stage liver disease due to prolonged NRTI exposure will become more apparent. Early interventions that include liver biopsy and, perhaps, modification of the antiretroviral therapy regimen should be considered.

Acknowledgments

Potential conflicts of interest. R.A.R. and C.F.D.: no conflicts.

Rahim A. Remtulla² and Catherine F. Decker^{1,2}

¹Division of Infectious Diseases, ²Department of Internal Medicine, National Naval Medical Center, Bethesda, Maryland

References

- Guaraldi G, Squillacne N, Stentarelli C, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. *Clin Infect Dis* **2008**; *47*:250–7.
- McGovern B, Ditelberg JS, Taylor LE, et al. Hepatic steatosis is associated with fibrosis, nucleoside analog use, and hepatitis C virus genotype 3 infections in HIV-seropositive patients. *Clin Infect Dis* **2006**; *43*:365–72.
- Sulkowski MS, Mehta SH, Torbenson M, et al. Hepatic steatosis and antiretroviral drug use among adults coinfecting with HIV and hepatitis C virus. *AIDS* **2005**; *19*:585–92.
- Zeremski M, Talal AH. Dideoxynucleoside analogues should be used cautiously in patients with hepatic steatosis. *Clin Infect Dis* **2006**; *43*:373–6.
- Walker UA, Bauerle J, Laguano M, et al. Depletion of mitochondrial DNA in liver under antiretroviral therapy with didanosine, stavudine, or zalcitabine. *Hepatology* **2004**; *39*:311–7.
- Walker UA, Setzer B, Venhoff N. Increased long-term mitochondrial toxicity in combina-

tions of nucleoside analogue reverse-transcriptase inhibitors. *AIDS* **2002**; 16:2165–73.

7. Neuschwander-Tetri BE, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLS single topic conference. *Hepatology* **2003**; 37: 1202–19.

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Department of Defense, the Department of the Navy, or the naval services at large.

Reprints or correspondence: Dr. Catherine F. Decker, Div. of Infectious Diseases, National Naval Medical Center, 8901 Wisconsin Ave., Bethesda, MD 20889 (catherine.decker@med.navy.mil).

Clinical Infectious Diseases **2008**; 47:1233–4

This article is in the public domain, and no copyright is claimed. 1058-4838/2008/4709-0021

DOI: 10.1086/592352

Reply to Remtulla and Decker

TO THE EDITOR—We appreciate the correspondence by Remtulla and Decker [1] in response to our recent article in *Clinical Infectious Diseases* [2]. Remtulla and Decker profile 2 white, male, nonobese patients whose cases of nonalcoholic steatohepatitis (NASH) progressed to hepatic cirrhosis over a multiple-year period, during which time they received antiretroviral therapy regimens that included dideoxynucleoside analogues (stavudine or didanosine) and that suppressed HIV infection. In patient 2, liver biopsy findings were compatible with drug-induced liver disease.

We agree with Remtulla and Decker [1] that, as previously demonstrated by Herman and Easterbrook [3] and Nunez and Soriano [4], exposure to nucleoside analogues (such as zalcitabine, stavudine, zidovudine, and didanosine) is associated with liver mitochondrial toxicity resulting in microvesicular steatosis, lactic acidosis, and mitochondrial DNA depletion. These changes can evolve to fibrosis and macrovesicular steatosis with focal necrosis.

In our analysis, the patients' cumulative median durations of exposure to stavudine and didanosine were just 51 and 31 months, respectively, and nearly one-half of patients had never been exposed to those drugs. Our own data clearly suggest

an etiologic role for prolonged NRTI exposure in the development of nonalcoholic fatty liver disease (NAFLD), but we did not discern progression to NASH or overt cirrhosis, because we did not perform consecutive liver biopsies. We surmise that it is possible that some patients with such drug exposure can indeed experience progression to hepatic cirrhosis.

Several issues are worthy of consideration:

1. The modalities used to monitor the progression from NAFLD to NASH—modalities that increasingly include non-invasive techniques, such as liver elastometry and fibroscan assessments—are diagnostic interventions in evolution that are commonly compared to liver biopsy. Liver biopsy remains a gold standard, although sampling error is a concern [5], especially if differential involvement with NAFLD or NASH occurs in various anatomic liver regions. Given the improved prognosis of HIV infection and the differential histologic pattern of metabolic (macrovesicular) and toxic (microvesicular) liver injury, it would be advisable to perform liver biopsies for patients more often than is done now [6].

2. The determinants of progression of metabolic fatty liver disease in HIV-infected individuals are poorly characterized. Although long-term NRTI treatment is likely a factor, pathophysiologic processes other than mitochondrial toxicity are likely involved. Experience with HIV-uninfected patients who have NAFLD suggests that insulin resistance may be a major determinant of disease progression [7]. However, whether this also occurs in HIV-infected persons remains to be ascertained.

3. Although our findings are consonant with observations made in the general population that persons with NAFLD experience low rates of progression to NASH and cirrhosis [8], we acknowledge that the “full story” of the continuum of liver disease among NRTI-treated patients, its causes, its patterns of progression, and

the optimal modalities for ongoing disease assessment remain to be fully elucidated.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

Giovanni Guaraldi,¹ Nicola Squillace,¹ Chiara Stentarelli,¹ Gabriella Orlando,¹ Stefano Zona,¹ Paola Loria,¹ and Frank Palella²

¹Department of Medicine, Infectious Diseases Clinic, University of Modena–Reggio Emilia School of Medicine, Modena, Italy; and ²Feinberg School of Medicine, Northwestern University, Chicago, Illinois

References

1. Remtulla AR, Decker CF. Nucleoside reverse-transcriptase inhibitor use, cirrhosis, and end-stage liver disease in HIV-infected patients. *Clin Infect Dis* **2008**; 47:1233–4.
2. Guaraldi G, Squillace N, Stentarelli C, et al. Nonalcoholic fatty liver disease in HIV-infected patients referred to a metabolic clinic: prevalence, characteristics, and predictors. *Clin Infect Dis* **2008**; 47:250–7.
3. Herman JS, Easterbrook PJ. The metabolic toxicities of antiretroviral therapy. *Int J STD AIDS* **2001**; 12:555–62; quiz 563–4.
4. Nunez M, Soriano V. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. *Drug Saf* **2005**; 28:53–66.
5. Ratziu V, Bugianesi E, Dixon J, et al. Histological progression of non-alcoholic fatty liver disease: a critical reassessment based on liver sampling variability. *Aliment Pharmacol Ther* **2007**; 26:821–30.
6. Brunt EM. Do you see what I see? The role of quality histopathology in scientific study. *Hepatology* **2008**; 47:771–4.
7. Loria P, Lonardo A, Carulli N. Should nonalcoholic fatty liver disease be renamed? *Dig Dis* **2005**; 23:72–82.
8. Adams LA, Lymp JF, St. Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* **2005**; 129:113–21.

Reprints or correspondence: Dr. Giovanni Guaraldi, Dept. of Medicine, Infectious Diseases Clinic, University of Modena–Reggio Emilia School of Medicine, Via del Pozzo 71, Modena, 41100 Italy (g.guaraldi@unimo.it).

Clinical Infectious Diseases **2008**; 47:1234

© 2008 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2008/4709-0023\$15.00

DOI: 10.1086/592353

Smartphone Utilities for Infectious Diseases Specialists

TO THE EDITOR—I read with interest the

invited article by Burdette et al. [1] on the use of a combined cellular telephone, pager, and personal digital assistant (i.e., a “smartphone”) in clinical practice. As a practicing physician and smartphone user, I will add some details to those included in the excellent overview by Burdette et al. [1].

First, the authors do not discuss the importance of having a global positioning system (GPS)-enabled smartphone for the infectious diseases specialist. Either a smartphone connected to an external GPS antenna via Bluetooth technology or a more modern and expensive smartphone with an integrated GPS antenna can allow quicker and easier location of patients in an epidemic. Navigators are usually integrated in smartphones with an internal GPS antenna, and they can make it easier to find an incident location. In addition, many freeware packages exist for tracking offroad points and paths (e.g., NoniGPSPlot [2]), and they are easily shared after converting into the widespread Google Earth (.kml) format, which can immediately be uploaded (together with photos or videos of patients taken with the integrated camera) to Web portals for access by other physicians. For those who cannot afford a GPS antenna and/or on-payment navigation software packages, Google Mobile-Maps [3] can track approximate position via identification information from cell phone towers and can show maps when connected to the Internet, a capability that is, of course, available only in developed countries.

Second, although Burdette et al. [1] did not aim to write a complete review of available software packages, we believe that some packages (not listed in their table) have special merits and deserve to be cited for their usefulness to the infectious diseases specialist, as follows:

1. PubMed for Handhelds provides the Wireless System for Emergency Responders (WISER) [4], which allows identification of chemical and biological hazards on the basis of reported symptoms

and signs.

2. McGraw-Hill provides the free-ware Diagnosaurus [5], which can help with differential diagnosis.
3. National Center for Biotechnology Information Bookshelf provides a handheld edition of the well-known book *Medical Microbiology* by Samuel Baron [6].
4. BeastMaster.net [7] can make your smartphone produce sounds of frequencies useful to expel gnats, fleas, house gnats, mice, rats, martens, and cockroaches (7–20 KHz). This can be very useful in certain in-the-field situations.
5. Software packages such as HNHS-Soft Talking Dictionaries [8] provide very useful talking phrase books that can help in emergency medical situations and help with interviewing individuals who speak languages unknown to the clinician.

We definitively believe that a new era has come for this advanced technology, which can improve performance of daily tasks for almost every infectious diseases specialist.

Acknowledgments

Potential conflicts of interest. D.F.: no conflicts.

Daniele Focosi

Division of Hematology,
University of Pisa, Pisa, Italy

References

1. Burdette SD, Herchline TE, Oehler R. Practicing medicine in a technological age: using smartphones in clinical practice. *Clin Infect Dis* 2008; 47:117–22.
2. NoniGPSPlot. Available at: <http://aeguerre.free.fr/Public/PocketPC/NoniGPSPlot/EN/index.php>. Accessed 4 September 2008.
3. Google Mobile-Maps. Available at: <http://www.google.com/mobile/default/maps/index.html>. Accessed 4 September 2008.
4. WISER, the Wireless Information System for Emergency Responders. Available at: <http://wiser.nlm.nih.gov/>. Accessed 4 September 2008.
5. Diagnosaurus, version 2.0. Available at: <http://books.mcgraw-hill.com/medical/diagnosaurus/index.html>. Accessed 4 September 2008.

6. Baron S. *Medical microbiology*. Available at: <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mmed.TOC&depth=2>. Accessed 4 September 2008.
7. BeastMaster.net. Available at: http://classic.pocketgear.com/software_detail.asp?id=15470. Accessed 4 September 2008.
8. HNHS-Soft talking dictionaries. Available at: <http://www.hnhsoft.com/>. Accessed 4 September 2008.

Reprints or correspondence: Dr. Daniele Focosi, Div. of Hematology, University of Pisa, Via Roma 56, 56126 Pisa, Italy (dfocosi@tin.it).

Clinical Infectious Diseases 2008; 47:1234–5

© 2008 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2008/4709-0023\$15.00
DOI: 10.1086/592354

Relationship between Shingles (Varicella Zoster) and Hypercalcemia Not Found

TO THE EDITOR—We read with interest the article by Norman and Politz [1] about the increased incidence of shingles among patients with primary hyperparathyroidism. The authors found that the rate of shingles was 6-fold higher among patients with primary hyperparathyroidism than it was among age-matched historical control subjects. They concluded that hypercalcemia may play a central causal role in the development of shingles. If this was a common phenomenon, higher mean calcium levels would be expected in unselected patients with shingles, compared with patients without shingles. To test this hypothesis, we retrospectively studied all patients hospitalized with a diagnosis of shingles at the Department of Internal Medicine at our tertiary care hospital in eastern Switzerland during 2002–2007. Diagnoses, patient characteristics, and laboratory data (serum calcium, phosphate, creatinine, and albumin levels) were obtained from the clinical information system. We identified 76 consecutive cases of shingles in 73 patients. All 5786 patients who were admitted to the Department of Internal Medicine during 1 full year (2003) served as control subjects.

Of the 76 cases, 61 (80%) were coded as localized shingles of the trunk and extremities, 2 (3%) were coded as general-

ized shingles, and 13 (17%) presented as shingles of cranial nerves. Fifty-three cases (70%) presented as acute shingles at the time of hospital admission, 16 (21%) evolved during hospitalization, and the remaining 7 (9%) could not be categorized. Of the 73 patients, active malignancy was present in 25 (34%), 2 (3%) had a history of malignancy, and no malignancy was suspected in 46 (63%). The diagnosis of primary hyperparathyroidism was not made during the index hospitalization for any of these patients.

The mean age (\pm SD) of the patients was 70 ± 14.3 years, and the mean age (\pm SD) of the control subjects was 63 ± 16.2 years ($P < .001$). Female sex was more prevalent among patients than among control subjects (45 patients [59%] vs. 2384 control subjects [41%]; $P = .002$). The unadjusted mean calcium level (\pm SD) was 2.29 ± 0.18 mmol/L (9.18 ± 0.72 mg/dL) in patients and 2.32 ± 0.18 mmol/L (9.30 ± 0.72 mg/dL) in control subjects ($P = .4$). The mean phosphate level (\pm SD) was 1.15 ± 0.41 mmol/L (3.57 ± 1.27 mg/dL) in patients and 1.07 ± 0.32 mmol/L (3.32 ± 0.99 mg/dL) in control subjects ($P = .02$). The maximum calcium level in patients was 2.8 mmol/L (11.23 mg/dL). After multivariate adjustment for age, sex, and creatinine clearance, the mean serum albumin calcium level was 0.019 mmol/L (0.076 mg/dL) lower in patients than in control subjects ($P = .3$), and the mean phosphate level was 0.06 mmol/L (0.19 mg/dL) higher in patients than in control subjects ($P = .09$).

In our analysis, we could not identify a relationship between shingles and serum calcium level. Although our findings are limited to hospitalized patients, our results suggest that hypercalcemia is not a common finding in unselected patients with acute shingles.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

**Philippe Rafeiner, Samuel Henz,
and Katia Boggian**

Division of Infectious Diseases and Hospital
Epidemiology, Kantonsspital St. Gallen,
St. Gallen, Switzerland

Reference

1. Norman J, Politz D. Shingles (varicella zoster) outbreaks in patients with hyperparathyroidism and their relationship to hypercalcemia. *Clin Infect Dis* 2008;46:1452–4.

Reprints or correspondence: Dr. Philippe Rafeiner, Div. of Infectious Diseases and Hospital Epidemiology, Kantonsspital St. Gallen, Rorschacherstrasse 95, CH-9007 St. Gallen, Switzerland (philippe.rafeiner@kssg.ch).

Clinical Infectious Diseases 2008;47:1235–6

© 2008 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2008/4709-0024\$15.00
DOI: 10.1086/592356

Reply to Rafeiner et al.

TO THE EDITOR—The report by Rafeiner et al. [1] is interesting and appropriate in light of our recent report [2] that showed an increased incidence of shingles outbreaks among patients with elevated serum calcium levels caused by primary hyperparathyroidism. Rafeiner et al. [1] examined the relationship between shingles outbreaks and elevated calcium levels from a completely different perspective than that used in our investigation. Their findings are interesting but, in contrast to what the authors suggest, do not necessarily contradict our findings.

It is not surprising to us that a retrospective study involving hospitalized patients did not find the same conclusions as our prospective study. In our evaluation of nearly 3500 ambulatory patients per year for primary hyperparathyroidism, we learned that serum calcium levels measured in healthy ambulatory patients do not correlate with serum calcium levels measured in hospitalized patients [2]. In fact, we discounted the importance of (and often completely ignore) any serum calcium levels measured in hospitalized patients when we evaluated patients for the presence of hyperparathyroidism. Hospitalized patients typically receive intravenous fluids, medications, and other ongoing therapies that are notorious for

influencing serum calcium levels. Without controlling for these issues, we believe that serum calcium levels obtained from hospitalized patients are suspect, at best.

The major difference between our observations [2] and those of Rafeiner et al. [1] is that we looked prospectively at thousands of patients with elevated calcium levels caused by primary hyperparathyroidism who were otherwise healthy and fully ambulatory. We examined the incidence of shingles among these healthy patients with hyperparathyroidism within the previous year. In the report by Rafeiner et al. [1], they used an extensive database to find hospitalized patients who had been coded on the basis of their diagnosis of shingles, and the authors examined serum calcium levels in this collection of patients. In many cases, the diagnosis of shingles was a secondary diagnosis and was not the cause of the patient's hospitalization. In some cases, it seems clear that hyperparathyroidism was present in their patient population but was not diagnosed (e.g., presence of a calcium level of 2.8 mmol/L [11.3 mg/dL]).

One-third (34%) of the patients described by Rafeiner et al. [1] had received a concomitant diagnosis of active malignancy, whereas none of our patients had received this diagnosis. As mentioned in our article [2] and in others [3–5], the presence of malignancy is associated with an increase in the prevalence of shingles outbreaks, presumably because of the effect of malignancy on the immune system.

We believe that there is little doubt about the relationship between hypercalcemia and shingles outbreaks. Our practice is limited to parathyroid disease in the ambulatory context, and on a near weekly basis, we see patients who have had recent outbreaks of shingles. It is possible that the confounding issues of hospitalization and the treatments, medications, and fluids that hospitalization entails simply make studying this relationship in the hospitalized patient confusing. Rafeiner et al. [1] are to be commended for their report, but their methodology may prevent them

from seeing the relationship that we see on a regular basis.

Acknowledgments

Potential conflicts of interest. J.N. and D.P.: no conflicts.

James Norman and Douglas Politz

Norman Parathyroid Clinic, Tampa, Florida

References

1. Rafeiner P, Henz S, Boggian K. Relationship of shingles (varicella zoster) and hypercalcemia not found. *Clin Infect Dis* 2008; 47:1235–6.
2. Norman J, Politz D. Shingles (varicella zoster) outbreaks in patients with hyperparathyroidism and their relationship to hypercalcemia. *Clin Infect Dis* 2008; 46:1452–4.
3. Donahue, JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med* 1995; 155:1605–9.
4. Weaver BA. The burden of herpes zoster and postherpetic neuralgia in the United States. *J Am Osteopath Assoc* 2007; 107(Suppl 1):S2–7.
5. Martinez E, Domingo P. Herpes zoster–induced acute hyperparathyroid crisis. *Clin Infect Dis* 1992; 14:1270–1.

Reprints or correspondence: Dr. James Norman, Endocrine Surgery, Norman Parathyroid Clinic, 3238 Cove Bend Dr., Tampa, FL 33647 (jgnorman@tampabay.rr.com).

Clinical Infectious Diseases 2008; 47:1236–7

© 2008 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2008/4709-0025\$15.00
DOI: 10.1086/592357

The Role of Air Travel in the Spread of Mumps

TO THE EDITOR—We are writing to correct a misconception in the excellent editorial on the 2006 mumps resurgence that appeared in a recent issue of *Clinical Infectious Diseases* [1]. The author misinterpreted an announcement that the Centers for Disease Control and Prevention was undertaking contact investigations for 2 passengers who had traveled by air while in the communicable period for mumps [2] as indicating that exposure to mumps on airplanes was a significant factor in the spread of the outbreak. However, these investigations evaluated the risk of mumps transmission during air travel, not the role that air travel played in the spread of mumps nationally or globally [3].

Air travel is recognized as a significant factor in the spread of infectious diseases

around the world [4, 5]. The strain of mumps virus associated with the 2006 US outbreak, genotype G, was the same strain that caused a large outbreak in the United Kingdom in 2005 [6]; therefore, the mumps virus responsible for the 2006 US mumps resurgence may have been introduced into the United States from the United Kingdom, presumably by air travel, which is the most common form of transatlantic travel. However, to our knowledge, there is no evidence specifically linking an infectious air traveler with the spread of mumps in the United States during the 2006 mumps resurgence.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

Karen J. Marienau,¹ Francisco Averhoff,¹ and Susan Redd²

¹National Center for Preparedness, Detection, and Control of Infectious Diseases, Division of Global Migration and Quarantine, Quarantine and Border Health Services Branch, and ²National Center for Respiratory Infectious Diseases, Division of Viral Diseases, Epidemiology Branch, Centers for Disease Control and Prevention, Atlanta, Georgia

References

1. Baum SG. Who cares about mumps? You should! *Clin Infect Dis* 2008; 46:1450–1.
2. Centers for Disease Control and Prevention. Exposure to mumps during air travel—United States, April 2006. *MMWR Morb Mortal Wkly Rep* 2006; 55:401–2.
3. Marienau KJ. Mumps transmission unlikely in flights under five hours [abstract 2050]. In: Program and abstracts of the Council of State and Territorial Epidemiologists Annual Conference, Atlantic City, NJ, 2007. Available at: <http://www.cste.org/annualconference/abstracts/absbookpb-id.pdf>. Accessed 12 September 2008.
4. Martinez L. Global infectious disease surveillance. *Int J Infect Dis* 2000; 4:222–8.
5. Freedman DO, Weld LH, Kozarsky PE, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med* 2006; 354:119–30.
6. Dayan GH, Quinlisk MP, Parker AA, et al. Recent resurgence of mumps in the United States. *N Engl J Med* 2008; 358:1580–9.

Reprints or correspondence: Dr. Karen J. Marienau, Centers for Disease Control and Prevention, National Center for Preparedness, Detection, and Control of Infectious Diseases, Div. of Global Migration and Quarantine, Quarantine and Border Health Services Branch, Atlanta, GA (kqm5@cdc.gov).

Clinical Infectious Diseases 2008; 47:1237

This article is in the public domain, and no copyright is claimed. DOI: 10.1086/592355

Active Surveillance Cultures for Methicillin-Resistant *Staphylococcus aureus* in an Intensive Care Unit

TO THE EDITOR—In the review by McGinagle et al. [1], the authors were unable to include our recently published studies [2, 3]. In our studies, the aim was to prevent the nosocomial spread of methicillin-resistant *Staphylococcus aureus* (MRSA) in our intensive care unit (ICU) by use of a screening approach. The project was also initiated to enable our hospital to meet the requirements of the nationwide “search and destroy” policy of The Netherlands.

The successful containment of MRSA in Dutch hospitals is attributable mainly to the strict isolation of all patients with known or suspected MRSA colonization. Our Regional Public Health Laboratory is located in an 800-bed teaching hospital in the Limburg Parkcity Heerlen, ~15 km from Charlemagne’s Aachen, which is part of the Euregio Rhine-Meuse, with ~250,000 inhabitants. This laboratory, which is located at the Atrium Medical Centre in Parkcity, also serves nursing homes and general practitioners.

Since 1999, MRSA multilocus sequence type 5 has been predominant in our region. The ICU is considered a high-risk department for the dissemination of MRSA. After an outbreak of infection due to multidrug-resistant *Acinetobacter baumannii* in 2001 [4], culture screening for multidrug-resistant microorganisms, including MRSA, was implemented for patients on admission to the ICU. During the *A. baumannii* outbreak, rapid detection of cases combined with hygienic preventive measures curbed the dissemination of this pathogen in the ICU. Consequently, this strategy has been generally applied in the ICU. The screening of patients on admission to the ICU has revealed the hidden carriage of MRSA. With a mean of 3 patients found to be carriers of MRSA per year, we detected 15 patients (0.21%) who carried MRSA of ~7000 patients admitted to the ICU

during the study period. A regional survey on MRSA performed in 2005 by the Public Health Authorities revealed that the prevalence of MRSA carriage in the randomly sampled general population was 0.08% (2 of 2500 individuals), 2–3-fold lower than the prevalence in our study [5]. The prevalence of MRSA carriage of 0.2% at our ICU is markedly lower than the 6.9% observed by Lucet et al. [6] among 2400 screened patients in 14 ICUs in France in 2003. We consider the approach of active selective screening of patients to be useful in a high-risk department such as the ICU, because active surveillance has been shown to decrease the incidence of MRSA infection elsewhere [7].

Active surveillance has prevented outbreaks in our ICU, after 3 outbreaks of infection due to multidrug-resistant bacteria in the years before its implementation. The 0.2% prevalence of MRSA among patients on admission to our ICU was 7-fold higher than that found during a previous screening for MRSA among hospital-admitted patients performed 5 years earlier elsewhere in The Netherlands, which demonstrated a low prevalence rate of 0.03% [8]. Weighing the costs of a pre-screening program for all or for a selected group of hospital-admitted patients versus the cost of unexpected epidemics will be necessary to optimize or refine a prevention strategy.

The current MRSA policy has been reconfirmed recently by a report released by The Netherlands National Health Council in November 2006 [9]. McGinagle et al. [1] defined the Dutch policy as the most aggressive approach and not one that is generally applicable in other settings. In view of the calculated higher costs of early closures of our ICU versus the cost of our targeted admission culture-screening program, our goal was fulfilled in the department most susceptible to MRSA outbreaks, the ICU.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

Johan H. T. Wagenvoort,¹ Els I. De Brauwer,¹ Jo M. Gronenschild,¹ Hub J. Toenbreker,² and Anita M. Schopen²

Departments of ¹Medical Microbiology and ²Hygiene and Infection Prevention, Atrium mc Parkstad, Heerlen, The Netherlands

References

1. McGinagle KL, Gourlay ML, Buchanan IB. The use of active surveillance cultures in adult intensive care units to reduce methicillin-resistant *Staphylococcus aureus*-related morbidity, mortality, and costs: a systematic review. *Clin Infect Dis* 2008;46:1717–25.
2. Wagenvoort JHT, De Brauwer EIGB, Klaassen CHW, et al. Kontrolle des epidemischen Auftretens eines multiresistenten *Acinetobacter baumannii*-Stamms. *Hyg Med* 2006;31:94–102.
3. Wagenvoort JHT, De Brauwer EIGB, Toenbreker HJM, Schopen AMH, Gronenschild JMH. The recall-screening for MRSA prevention—an innovative approach from the Netherlands. *Hyg Med* 2008;33:10–5. Available at: http://www.mhp-verlag.de/en/zeitschriften/kopie_von_hygmed0102_08_1.shtml. Accessed 18 September 2008.
4. Wagenvoort JHT, De Brauwer EIGB, Toenbreker HMJ, van der Linden CJ. Epidemic *Acinetobacter baumannii* strain with MRSA-like behaviour carried by healthcare staff. *Eur J Clin Microbiol Infect Dis* 2002;21:326–7.
5. Ten Ham PB, Hoebe CP, Nys S, Driessen C, Deurenberg RH, Stobberingh EE. Prevalence of antibiotic resistance in the community [poster 168]. In: Programs and abstracts of the 12th International Symposium on Staphylococci and Staphylococcal Infections (The Netherlands). 2006.
6. Lucet JC, Chevret S, Durand-Zaleski I, Chastang C, Regnier B; Multicenter Study Group. Prevalence and risk factors for carriage of methicillin-resistant *Staphylococcus aureus* at admission to the intensive care unit: results of a multicenter study. *Arch Intern Med* 2003;163:181–8.
7. Huang SS, Yokoe DS, Hinrichsen VL, et al. Impact of routine intensive care unit surveillance cultures and resultant barrier precautions on hospital-wide methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2006;43:971–8.
8. Wertheim HF, Vos MC, Boelens HA, et al. Low prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) at hospital admission in The Netherlands: the value of search and destroy and restrictive antibiotic use. *J Hosp Infect* 2004;56:321–5.
9. Health Council of The Netherlands 2006. MRSA policy in The Netherlands. Publication no. 2006/17. Available at: <http://www.healthcouncil.nl/pdf.php?ID=1456&p>. Accessed 16 September 2008.

Reprints or correspondence: Dr. Johan H. T. Wagenvoort, Dept. of Medical Microbiology, Atrium mc Parkstad, Heerlen, Postbox 4446, 6401 CX Heerlen, The Netherlands (medische.microbiologie@atriummc.nl).

Clinical Infectious Diseases 2008;47:1237–8

© 2008 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2008/4709-0027\$15.00
DOI: 10.1086/592358

Methicillin-Resistant *Staphylococcus aureus*: Misinterpretation and Misrepresentation of Active Detection and Isolation

TO THE EDITOR—McGinagle et al. [1] concluded that recent studies regarding the control of methicillin-resistant *Staphylococcus aureus* (MRSA) were not high quality, because “none of the studies used randomly assigned controls” [1, p. 1722]. Because of their expressed interest in quality and because this was their first publication about MRSA or infection control listed on Medline, we thought that they would appreciate hearing about some of their own errors and misinterpretations (all of which cannot be addressed in a letter).

McGinagle et al. [1] indicated that they reviewed the use of active surveillance cultures as advocated by the 2003 Society for Healthcare Epidemiology of America (SHEA) guideline [2], but they apparently failed to grasp that the guideline recommended active detection and isolation (ADI) as a combined measure. McGinagle et al. [1] claimed to have evaluated 16 such studies, but they actually reviewed 13; 3 of the studies that they evaluated did not examine the efficacy of ADI.

McGinagle et al. [1] inaccurately represented a study by Huang et al. [3]. McGinagle et al. [1] reported that the “detection of MRSA infections increased by 30%–135% with [active surveillance cultures]” [1, p. 1720]; what actually increased was the detection of patients colonized with MRSA (most of whom usually go undetected by routine clinical cultures).

McGinagle et al. [1] also misrepresented another study by Huang et al. [4], reporting that MRSA bacteremia decreased

by 75% in the hospital ICUs with ADI and by 40% “in the remainder of the hospital that was not receiving the intervention” [1, p. 1719]. Controlling the spread of MRSA in the ICU decreased the spread to other wards; when patients colonized by MRSA were transferred to other wards, they remained isolated, and an electronic database was used to ensure the reisolation of the patient on readmission. Each measure likely contributed to the 40% reduction in MRSA bacteremia on non-ICU wards.

McGinagle et al. [1] inaccurately stated that another study showed a 14% reduction in MRSA acquisition, from 5.6 to 1.4 cases per 100 admissions [5]; these data show a 75% (not 14%) relative reduction in MRSA prevalence. In addition, this was cited in the study’s discussion section (not the results) [5], and these data were from a prior study at the same hospital [6], which was ignored in the review.

McGinagle et al. [1] indicate that it is unclear which patients to screen. The SHEA guideline [2] recommends finding and isolating all individuals colonized with MRSA. Each facility should use a screening program and clinical microbiology data to do this, and they should flexibly adjust screening criteria because situations—and thus optimal criteria—will vary by time and place.

We will not dignify the authors’ repetition of the usual litany of nihilists’ arguments against the use of ADI in MRSA control with a comment. McGinagle et al. [1] fail to recognize that ADI has worked against tuberculosis, smallpox, and severe acute respiratory syndrome [7], and it will be used if pandemic avian influenza should occur.

McGinagle et al. [1] state that “a randomized, controlled trial to prove the efficacy of [active surveillance cultures] would be helpful” [1, p. 1723]. A single study of any design does not prove a hypothesis, it just alters the probability of correctness. Randomized and nonrandomized studies examining the same questions demonstrated similar results in

recent meta-analyses [8, 9]. A poorly conducted randomized trial [10, 11] (e.g., with suboptimal power; delayed screening, specimen processing, and isolation implementation; failure to screen most colonized patients; etc.) will not add accurate data.

McGinagle et al. [1] mention superb MRSA control in northern European countries [12] where ADI is used routinely, but they fail to note similar control in Western Australia [13] or that the control has been sustained over decades on both continents. They also do not mention the much higher rates of nosocomial MRSA infection in all other European countries and Australian states that do not routinely use ADI. McGinagle et al. [1] speculate that successful control in northern Europe could be attributable to a low prevalence of MRSA. They fail to recognize that MRSA caused 33% of *S. aureus* bacteremias in Denmark before the introduction of ADI; the huge, multiyear Dutch hospital epidemic that occurred during a temporary suspension of effective ADI; or the large northern European epidemics of MRSA that were controlled with ADI [11].

Acknowledgments

Potential conflicts of interest. W.R.J. has served as a consultant for Johnson & Johnson, 3M, Pfizer, Kimberly-Clark, and Baxa. B.M.F.: no conflicts.

Barry M. Farr¹ and William R. Jarvis²

¹University of Virginia, Charlottesville; and ²Jarvis and Jason Associates, Hilton Head Island, South Carolina

References

- McGinagle KL, Gourlay ML, Buchanan IB. The use of active surveillance cultures in adult intensive care units to reduce methicillin-resistant *Staphylococcus aureus*-related morbidity, mortality, and costs: a systematic review. *Clin Infect Dis* **2008**; *46*:1717–25.
- Muto CA, Jernigan JA, Ostrowsky BE, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and *Enterococcus*. *Infect Control Hosp Epidemiol* **2003**; *24*:362–86.
- Huang SS, Rifas-Shiman SL, Warren DK, et al. Improving methicillin-resistant *Staphylococcus aureus* surveillance and reporting in intensive care units. *J Infect Dis* **2007**; *195*:330–8.
- Huang SS, Yokoe DS, Hinrichsen VL, et al.

Impact of routine intensive care unit surveillance cultures and resultant barrier precautions on hospital-wide methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis* **2006**; *43*:971–8.

- Chaix C, Durand-Zaleski I, Alberti C, Brun-Buisson C. Control of endemic methicillin-resistant *Staphylococcus aureus*: a cost-benefit analysis in an intensive care unit. *JAMA* **1999**; *282*:1745–51.
- Girou E, Pujade G, Legrand P, Cizeau F, Brun-Buisson C. Selective screening of carriers for control of methicillin-resistant *Staphylococcus aureus* (MRSA) in high-risk hospital areas with a high level of endemic MRSA. *Clin Infect Dis* **1998**; *27*:543–50.
- Farr BM. Doing the right thing (and figuring out what that is). *Infect Control Hosp Epidemiol* **2006**; *27*:999–1003.
- Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* **2000**; *342*:1887–92.
- Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* **2000**; *342*:1878–86.
- Huskins WC, O’Grady NP, Samore M, Wallace D, Goldmann DA, Pappas PG. Design and methodology of the Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Intensive Care Units (STAR-ICU) trial. *Infect Control Hosp Epidemiol* **2007**; *28*:245–6.
- Farr BM. What to think if the results of the National Institutes of Health randomized trial of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* control measures are negative (and other advice to young epidemiologists): a review and an au revoir. *Infect Control Hosp Epidemiol* **2006**; *27*:1096–106.
- Tiemersma EW, Bronzwaer SL, Lyytikäinen O, et al. Methicillin-resistant *Staphylococcus aureus* in Europe, 1999–2002. *Emerg Infect Dis* **2004**; *10*:1627–34.
- Dailey L, Coombs GW, O’Brien FG, et al. Methicillin-resistant *Staphylococcus aureus*, Western Australia. *Emerg Infect Dis* **2005**; *11*:1584–90.

Reprints or correspondence: Dr. William R. Jarvis, Investigation and Prevention Branch, Jason and Jarvis Associates, 135 Dune Ln., Hilton Head, SC 29928 (wrjmj@aol.com).

Clinical Infectious Diseases **2008**; *47*:1238–9

© 2008 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2008/4709-0028\$15.00
DOI: 10.1086/592119

Reply to Farr and Jarvis

TO THE EDITOR—We read with interest the comments of Farr and Jarvis [1] regarding our recently published systematic review in *Clinical Infectious Diseases* [2]. We are unable to address all of their errors

and will concentrate on the most fundamental epidemiological principles relevant to the discussion.

Farr and Jarvis [1] questioned the criteria used to determine the quality ratings of the reviewed articles. We used the rating systems published by the UK National Health Service Centre of Reviews and Dissemination and the US Preventive Services Task Force [3, 4], which is the leading independent panel of private-sector experts in prevention and primary care in the United States. On the basis of these rigorous and widely respected quality-rating systems, in which randomized, controlled design is an important criterion, all of the reviewed articles were determined to be of fair or poor quality. Of note, 14 of the 16 reviewed observational studies lacked control groups, making their dramatic results difficult to interpret. Farr and Jarvis [1] did not specify a recommended source for quality ratings, so we are unable to assess their criteria for evidence grading.

We are puzzled and dismayed by the Farr and Jarvis's comment that "randomized and nonrandomized studies examining the same questions demonstrated similar results in recent meta-analyses" [1, p. 1239]. Discordance in results from randomized trials and observational studies is well documented by examples such as the Women's Health Initiative [5] and the Cardiac Arrhythmia Suppression Trial [6], which were randomized, controlled trials (RCTs) that strongly contradicted the purported cardiovascular benefits from vitamin E [7]. We note that Farr and Jarvis [1] presented a similar argument in a recent publication: "Recent meta-analyses of RCTs found that their results showed as much and sometimes more variability than did those from nonrandomized studies examining the same question, which neither overestimated nor underestimated the central tendency of the RCT results" [8, p. 154]. Farr and Jarvis [1] seem to imply that observational studies are "good enough" to estimate the results of RCTs, even though exposed and unexposed patients in a nonrandomized study may

have a different risk of the target outcome at baseline. We maintain that randomized, placebo-controlled design is the gold standard for intervention trials [9]. We are concerned to see any researcher downplay the importance of randomized design, even if randomized trials are unfeasible for certain research topics.

We concluded in our review that "Evidence from multiple observation-based studies suggests that the use of [active surveillance cultures] reduces the incidence of [methicillin-resistant *Staphylococcus aureus*] infection, but the overall quality of the evidence is poor; thus, definitive, evidence-based clinical recommendations cannot be made" [2, p. 1723]. This conclusion simply reflects the state of current research as judged by the rigorous criteria mentioned above; it is not "nihilistic." We discussed the great successes of active surveillance culture programs in other countries, and we applaud US health care centers that are attempting to use active surveillance culture programs to achieve better infection control. Although flexibility is important, many details of active surveillance culture implementation require a stronger evidence base to assist all kinds of health care centers with infection control. We hope our review may prompt other researchers to design stronger observational or randomized studies that will clarify the most efficient and cost-effective approaches to reducing MRSA infection rates in our hospitals and communities.

Acknowledgments

Potential conflicts of interest. K.L.M. and M.L.G.: no conflicts.

**Katharine L. McGinagle
and Margaret L. Gourlay**

University of North Carolina, Chapel Hill

References

1. Farr BM, Jarvis WR. Methicillin-resistant *Staphylococcus aureus*: misrepresentation and misinterpretation of active detection and isolation. *Clin Infect Dis* 2008; 47:1238–9 (in this issue).
2. McGinagle KL, Gourlay ML, Buchanan IB. The use of active surveillance cultures in adult intensive care units to reduce methicillin-resistant

Staphylococcus aureus-related morbidity, mortality, and costs: a systematic review. *Clin Infect Dis* 2008; 46:1717–25.

3. NHS Centre for Reviews and Dissemination (CRD). Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews, report 4. 2nd ed. York, UK: University of York, 2001.
4. Saha S, Hoerger TJ, Pignone MP, Teutsch SM, Helfand M, Mandelblatt JS. The art and science of incorporating cost effectiveness into evidence-based recommendations for clinical preventive services. *Am J Prev Med* 2001; 20(Suppl 3):36–43.
5. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321–33.
6. The Cardiac Arrhythmia Suppression Trial (CAST) investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med* 1989; 321:406–12.
7. Tatsioni A, Bonitsis NG, Ioannidis JP. Persistence of contradicted claims in the literature. *JAMA* 2007; 298:2517–26.
8. Farr BM, Bellingan G. Pro/con clinical debate: isolation precautions for all intensive care unit patients with methicillin-resistant *Staphylococcus aureus* colonization are essential. *Crit Care* 2004; 8:153–6.
9. Guyatt G, Drummond R, eds. Users' guides to the medical literature: essentials of evidence-based clinical practice. Chicago: AMA Press, 2002:442.

Reprints or correspondence: Dr. Katharine L. McGinagle, University of North Carolina Healthcare, 101 Manning Dr., Chapel Hill, NC 27514 (kmcginig@unch.unc.edu).

Clinical Infectious Diseases 2008; 47:1239–40

© 2008 by the Infectious Diseases Society of America. All rights reserved. 1058-4838/2008/4709-0029\$15.00
DOI: 10.1086/592120