Gastric Acid–Suppressive Agents and Risk of *Clostridium difficile*–Associated Disease

To the Editor: Dr Dial and colleagues have reported on the rate of *Clostridium difficile*–associated disease (CDAD) in the United Kingdom.[1] Their study is notable because this is the first time that pathology laboratory data from the UK General Practice Research Database (GPRD) have been used as an outcome of interest in a pharmacoepidemiological study. Moreover, the study may have important clinical implications.

As the authors acknowledge, the striking exponential rise in the rate of community-acquired CDAD diagnosed since 1994 may be partly due to increased reporting and testing. However, there have been major changes in the UK health care system and GPRD in the reporting and collection of CDAD that need to be considered when interpreting the results. In the UK, data from the local pathology laboratory are either sent to a general practice via an electronic link and then loaded in the patient's record electronically, or sent by mail and then entered manually.[2] There have been major improvements over time in electronic linkage of information between laboratory and general practice. Electronic collection of laboratory test data are more efficient for general practitioners compared with the manual procedure. Furthermore, it has recently become mandatory that laboratory test results are coded with Read medical codes. However, the Read medical codes for the CDAD toxin assay only became available to pathology laboratories in March 2002.[3] Thus, the observed increase in the rate of CDAD infections may be explained by more frequent electronic data transfer rather than a true increase in the rate of infection. It would be of interest to evaluate whether the ratio of CDAD diagnoses based on laboratory records to the clinically recorded diagnoses varied over calendar time in GPRD.

The Health Protection Agency (HPA) collects national reports of *C difficile* for England, Wales, and Northern Ireland. This reporting was voluntary until January 2004 when it became mandatory for health professionals to report CDAD in patients aged 65 years and over. In both GPRD and HPA data sets, the reporting rates have increased dramatically over time (a 40-fold increase in national reporting to the HPA from 1990-2004).[4] Nevertheless, the pattern of increases varied between GPRD and HPA, suggesting improvements in GPRD data collection. Importantly, the HPA concluded that the apparent increase in reporting rates of *C difficile* infections was thought to be due to improvements in reporting.[5] We feel therefore that the apparent time trends of the *C difficile* infections as presented by Dial et al could be in part an artifact and that these results should be interpreted with great caution.

Tjeerd-Pieter van Staa, MD, PhD
tjeerd.vanstaa@mhra.gsi.gov.uk
General Practice Research Database
London, England

Frank de Vries, MSc
Hubert G. M. Leufkens, PhD
Utrecht Institute for Pharmaceutical Sciences
Utrecht University
Utrecht, the Netherlands

Financial Disclosures: None reported.

1. Dial S, Delaney JAC, Barkun AN, Suissa S. Use of gastric acid–suppressive agents and the risk of community-acquired *Clostridium difficile*–associated *disease*. *JAMA*. 2005;294:2989-2995.
2. In Practice Systems Training Services. Pathology results and mailbox and mail administrator. In: In Practice Systems Training Services, Vision3 Training Guide (08/07/03). Available at: http://www.inps.co.uk/visiontrainingguide/11v3tgma.pdf. Accessed December 21, 2005.
3. NHS Connecting for Health Clinical Terminology Service. Pathology bounded code list (PBCL) of Read codes for pathology report messages version 1.012 July 2005. Available at http://www.connectingforhealth.nhs.uk/pathology/tech_standards/docs/bl1012.zip. Accessed December 21, 2005.
4. Health Protection Agency. Reports of Clostridium difficile isolated from faecal specimens under the voluntary reporting system: England, Wales, and Northern Ireland 1990-2004. Health Protection Agency UK Web Site. Available at: http://www.hpa.org.uk/infections/topics_az/clostridium_difficile/vol_data.htm. Accessed January 5, 2006.
5. Health Protection Agency. Voluntary reporting of *Clostridium difficile*, England, Wales, and Northern Ireland: 2004. *Commun Dis Rep CDR Wkly*. 2005; 15:1-3.

To the Editor: Dr Dial and colleagues[1] studied the risk of developing CDAD in individuals who were taking acid antisecretory agents. We have major concerns regarding the validity of the CDAD diagnoses and inadequate controlling for confounding variables.

The most striking finding of this study was that, of the 1233 patients with community-acquired CDAD, 791 (64%) had no apparent exposure to antibiotics in the preceding 90 days. Although the authors note several possible reasons for this result, the finding is difficult to reconcile with data from other studies. Hirschhorn et al[2] performed a health maintenance organization-based study of community-

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Letters Section Editor: Robert M. Golub, MD, Senior Editor.

acquired CDAD and found that 33 of the 51 community-acquired CDAD cases (65%) had antibiotics dispensed from one of the health maintenance organization pharmacies in the preceding 6 weeks alone. Noren et al[3] found that in a cohort of 372 patients with CDAD, in which 59 cases were community-acquired, 98% had received antibiotics within the previous 90 days.

Additionally, of the 1233 community-acquired CDAD episodes, 400 were diagnosed clinically without the use of a *C difficile* toxin assay, and many without a recognized risk factor for CDAD. We are not aware of previous studies of the accuracy of clinical diagnosis of CDAD under these circumstances, and believe that it is questionable.

Another critical issue is the lack of adjustment for global comorbidity, since an association between risk of CDAD and disease severity and comorbidity has been reported.[4,5] Coexistent disease may act as a confounding variable if acid antisecretory drug use is more common in individuals with multiple comorbidities, as these studies suggest. Although the authors do control for several individual coexisting illnesses, they do not use any general measure of comorbidity such as the Charlson Index. To this end, Pepin et al[4] did find an increased relative risk of 1.67 and 1.53 of CDAD with proton pump inhibitors and H2 blockers, respectively, on univariate analysis. However, this became insignificant (relative risk of 1.0 and 1.07, respectively) upon multivariate analysis that included an adjustment for the Charlson Index. Kyne et al[5] similarly found a relative risk of CDAD of 2.2 with acid antisecretory therapy ($P=.05$), but this regressed toward the null on multivariate analysis.

For these reasons, we do not believe that this study provides strong evidence of increased risk of CDAD associated with acid antisecretory therapy.

Daniel Leffler, MD, MS
dleffler@caregroup.harvard.edu
Department of Gastroenterology
Jeffery W. Cloud, MD
Department of Infectious Disease
Ciaran P. Kelly, MD
Department of Gastroenterology
Beth Israel Deaconess Medical Center
Boston, Mass

Financial Disclosures: Dr Leffler reported working as a speaker for SynSorb Biotech Inc and Astra-Hellas; a consultant for GalaGen Inc, Chiron, Millennium Pharmaceuticals, Ross Products, Abbott Laboratories, Biocodex Laboratories, Genentech Inc, Genome Therapeutics, Inc; and providing research support for GalaGen Inc, Biocodex Laboratories, and Janssen Pharmaceutica. None reported by Dr Cloud. Dr Kelly reported working as a speaker for Salix Pharmaceuticals, ViroPharma Inc, and Robert Michael Communications; a consultant and scientific advisor for Acambis Inc, ActivBiotics Inc, Cambridge Antibody Technology Ltd, Genzyme Inc, LumeRx, Massachusetts Biologics Laboratories, Salix Pharmaceuticals, Trine Pharmaceuticals, Ivpcare Inc, MPM Asset Management LLC, Oscient Pharmaceuticals, ViroPharma Inc, Gerson Lehrman Group, Frazier Healthcare Ventures; and providing research support for Acambis, ActivBiotics Inc, Cambridge Antibody Technology Ltd, Massachusetts Biologics Laboratories, and Salix Pharmaceuticals.

1. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid–suppressive agents and the risk of community-acquired *Clostridium difficile*–associated disease. *JAMA*. 2005;294:2989-2995.

2. Hirschhorn LR, Trnka Y, Onderdonk A, Lee ML, Platt R. Epidemiology of community-acquired *Clostridium difficile*–associated diarrhea. *J Infect Dis*. 1994;169:127-133.

3. Noren T, Akerlund T, Back E, et al. Molecular epidemiology of hospital-associated and community-acquired *Clostridium difficile* infection in a Swedish county. *J Clin Microbiol*. 2004;42:3635-3643.

4. Pepin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*–associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis*. 2005;41:1254-1260.

5. Kyne L, Sougioultzis S, McFarland LV, Kelly CP. Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea. *Infect Control Hosp Epidemiol*. 2002;23:653-659.

In Reply: With regard to the comments by Dr van Staa and colleagues, the effect of reporting and the effect of increasing numbers of *C difficile* cases are difficult to disentangle. We agree that the magnitude of the rise we described needs to be interpreted with caution. Nevertheless, our analysis controlled for the impact of such potential reporting trends by matching on calendar time.

Dr Leffler and colleagues raise a number of issues. First, regarding antibiotic use, the 2 studies that they cite are much smaller than ours, but nonetheless support the concept that community-acquired CDAD does occur and that prior antibiotic exposure may be less frequent in that setting. Most studies are on nosocomial CDAD where antibiotic use is very prevalent, and we calculated a pooled prevalence of 72% antibiotic exposure in controls with a corresponding 96% exposure in CDAD cases in these studies. This high prevalence of antibiotic exposure in nosocomial CDAD has contributed to the belief that antibiotics are a prerequisite; this may have contributed to ascertainment bias, with patients with prior antibiotic exposure more likely to be tested and diagnosed. Antibiotic use in the community is significantly lower and in 3 case-control studies where 15% or less of the controls had prior antibiotic exposure, only 49%[1], 50%[2] and 52%[3] of the cases had prior antibiotic exposure.

Second, the patients with a "clinical diagnosis" were cases without a diagnostic test in the medical record. With the current understanding of CDAD[4], it seems unlikely that physicians would make a clinical diagnosis of CDAD without a positive toxin, particularly in patients without recent antibiotic exposure, so we believe that these patients were toxin-positive but the result was not recorded. Regardless, our sensitivity analyses examining toxin-diagnosis and clinical-diagnosis results separately showed almost identical risks associated with proton pump inhibitor exposure.

Finally, we carefully and specifically adjusted for many important comorbid illnesses, including many that are in the Charlson Index. In order to hypothesize a priori that an adjusting index is useful, it would be important to identify additional illnesses that might be related to both proton pump inhibitor use and CDAD, and directly determine the potential confounders rather than speculate on possible poorly defined or justified risk factors to explain this association. Important limitations of the study by Pepin et al were addressed in our article; whatever concerns there

may be about confounding of the association with gastric acid suppression and CDAD, antibiotic exposure in hospitalized patients is likely more confounded.

Sandra Dial, MD, MSc
sandra.dial@mcgill.ca
Division of Critical Care and Respiratory and Clinical Research
J. A. C. Delaney, MSc
Alan N. Barkun, MD, MSc
Samy Suissa, PhD
Division of Clinical Epidemiology
McGill University Health Centre
Montreal, Quebec

Financial Disclosures: Dr Barkun reported being a consultant for AstraZeneca Inc and Altana Pharma Inc. No other authors reported financial disclosures.

1. Simor AE, Yake SL, Tsimidis K. Infection due to *Clostridium difficile* among elderly residents of a long-term-care facility. *Clin Infect Dis*. 1993;17:672-678.
2. Wilcox MH, Bendall R, Settle CD, Fawley WN. Community *Clostridium difficile* infection. Abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; L768, 441, 2001.
3. Blot E, Escande MC, Besson D, et al. Outbreak of *Clostridium difficile*-related diarrhoea in an adult oncology unit: risk factors and microbiological characteristics. *J Hosp Infect*. 2003;53:187-192.
4. Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J Jr. *Clostridium difficile*–associated diarrhea and colitis. *Infect Control Hosp Epidemiol*. 1995;16:459-477.

Carbon Monoxide Poisoning, Myocardial Injury, and Mortality

To the Editor: The study by Mr Henry and colleagues[1] concluded that there is an association between moderate to severe carbon monoxide (CO) exposure and myocardial injury. However, in addition to CO, cyanide exposure should be considered in individuals who present in extremis or with a severe metabolic acidosis following fire exposure.[2] It is not stated in the article which of the patients had fire exposure. It would be valuable to know which patients in this cohort were exposed to fire, which had lactic acidosis, which had elevated cyanide levels, and which patients received sodium thiosulfate antidote therapy, to determine whether a link can be made between cyanide and myocardial injury.

Gar Ming Chan, MD
garchan@pol.net
North Shore University Hospital
Department of Emergency Medicine
Manhasset, NY

Financial Disclosures: None reported.

1. Henry CR, Satran D, Lindgren B, Adkinson C, Nicholson CI, Henry TD. Myocardial injury and long-term mortality following moderate to severe carbon monoxide poisoning. *JAMA*. 2006;295:398-402.
2. Baud FJ, Barriot P, Toffis V, et al. Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med*. 1991;325:1761-1766.

To the Editor: Mr Henry and colleagues[1] studied long-term mortality among a large group of patients with CO poisoning. There are several issues in their study that we believe need to be addressed.

The authors previously identified subsets of these patients with significant age and echocardiogram differences (global vs regional wall motion abnormality), suggesting that the former experienced CO-related "stunned myocardium," while the latter had "unmask[ed] underlying CAD."[2] Did the mortality rates in these 2 groups differ at follow-up? The statistically significant mortality differences in the univariable analyses of previous diabetes, hypertension, and prior history of congestive heart failure or coronary artery disease as predictors in the present study would support such a difference. Was there any difference between patients with and without initial myocardial injury in their reported duration of CO exposure? Furthermore, while it is not clear if "time is muscle" applies to CO-induced myocardial injury, did door-to-chamber time or exposure-to-chamber time correlate with initial myocardial injury or outcome?

The reported long-term follow-up was completed using the Social Security Death Index. While the National Death Index has been documented to accurately identify individuals who have died,[3] the actual attribution of cause of death may be inadequate, particularly when autopsy information is not available.[4] Unrecognized completed suicide may have been miscoded as "unknown causes" or "cardiovascular causes." Such a systematic bias would not be expected to disproportionately affect patients with markers of cardiac injury at the time of their CO exposure unless these groups were different at baseline (eg, if suicidal patients are more likely to sustain myocardial injury because of prolonged CO exposure).

Although we agree that it is unclear whether interventions can affect short-term and long-term outcomes of patients who experience myocardial injury from CO poisoning, a single 90-minute treatment at 2.4 atmospheres absolute is less of a dose of oxygen and pressure than is administered by many hyperbaric centers.[5]

Until the relationships between CO poisoning, myocardial injury, time to treatment, and long-term risk of death are better delineated, we agree that it is prudent to perform some cardiac evaluation on selected patients. However, we believe that it is still unclear if CO-induced myocardial injury (particularly "stunned myocardium") is a predictor of long-term mortality.

Alberto Perez, MD
aaperez@harthosp.org
Kelly Johnson-Arbor, MD
Charles A. McKay, MD
Division of Medical Toxicology
Hartford Hospital
Hartford, Conn

Financial Disclosures: None reported.

1. Henry CR, Satran D, Lindgren B, Adkinson C, Nicholson CI, Henry TD. Myocardial injury and long-term mortality following moderate to severe carbon monoxide poisoning. *JAMA*. 2006;295:398-402.
2. Satran D, Henry CR, Adkinson C, Nicholson CI, Bracha Y, Henry TD. Cardiovascular manifestations of moderate to severe carbon monoxide poisoning. *J Am Coll Cardiol*. 2005;45:1513-1516.
3. Curb JD, Ford CE, Pressel S, Palmer M, Babcock C, Hawkins CM. Ascertainment of vital status through the National Death Index and the Social Security Administration. *Am J Epidemiol*. 1985;121:754-766.
4. Roulson J, Benbow EW, Hasleton PS. Discrepancies between clinical and autopsy diagnosis and the value of post mortem histology, a meta-analysis and review. *Histopathology*. 2005;47:551-559.
5. Hampson NB, Little CE. Hyperbaric treatment of patients with carbon monoxide poisoning in the United States. *Undersea Hyperb Med*. 2005;32:21-26.