Host and Pathogen Factors for Clostridium difficile Infection and Colonization

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ABSTRACT

BACKGROUND
Clostridium difficile infection is the leading cause of health care–associated diarrhea, and the bacterium can also be carried asymptptomatically. The objective of this study was to identify host and bacterial factors associated with health care–associated acquisition of C. difficile infection and colonization.

METHODS
We conducted a 15-month prospective study in six Canadian hospitals in Quebec and Ontario. Demographic information, known risk factors, potential confounding factors, and weekly stool samples or rectal swabs were collected. Pulsed-field gel electrophoresis (PFGE) was performed on C. difficile isolates to determine the genotype. Levels of serum antibodies against C. difficile toxins A and B were measured.

RESULTS
A total of 4143 patients were included in the study; 117 (2.8%) and 123 (3.0%) had health care–associated C. difficile infection and colonization, respectively. Older age and use of antibiotics and proton-pump inhibitors were significantly associated with health care–associated C. difficile infection. Hospitalization in the previous 2 months; use of chemotherapy, proton-pump inhibitors, and H₂ blockers; and antibodies against toxin B were associated with health care–associated C. difficile colonization. Among patients with health care–associated C. difficile infection and those with colonization, 62.7% and 36.1%, respectively, had the North American PFGE type 1 (NAP1) strain.

CONCLUSIONS
In this study, health care–associated C. difficile infection and colonization were differentially associated with defined host and pathogen variables. The NAP1 strain was predominant among patients with C. difficile infection, whereas asymptomatic patients were more likely to be colonized with other strains. (Funded by the Consortium de Recherche sur le Clostridium difficile.)


Clostridium difficile is the leading cause of health care–associated infectious diarrhea. After exposure to C. difficile, some patients remain asymptomatic, whereas others have illness ranging from mild diarrhea to fulminant colitis. 

Outbreaks of C. difficile infection in North America and Europe have been attributed to the emergence of an epidemic strain (North American pulsed-field gel electrophoresis [PFGE] type 1 [NAP1]).

Risk factors for C. difficile infection include antibiotic use, advanced age, increased severity of underlying illness, prior hospitalization, use of feeding tubes, gastrointestinal surgery, and use of proton-pump inhibitors. 

Variability in host factors may explain the wide spectrum of symptoms and course. Colonization with C. difficile and high levels of serum antibody against C. difficile toxin A appear to provide protection against C. difficile infection.

The best-described C. difficile virulence factors are toxins A and B. The genes encoding toxins A and B (tcdA and tcdB, respectively) are on the 19.6-kb so-called pathogenicity locus, along with two regulatory genes (tcdC and tcdR) and a gene (tcdE) encoding a protein proposed to function as a porin facilitating the release of toxins A and B. It was initially believed that toxin A was the most important toxin in C. difficile infection, but studies have shown that toxin B may be the more potent of the two toxins.

In addition, a binary toxin encoded by two genes (cdaA and cdbB) has been described in C. difficile. The cdbB product mediates cell-surface binding and intracellular translocation, and the product of cdaA disrupts actin-filament assembly; however, the clinical significance of binary toxin in C. difficile infection remains uncertain.

The objective of this study was to examine the relationships among host risk factors, bacterial virulence, and host immunity in health care–associated C. difficile infection and health care–associated asymptomatic colonization with C. difficile.

Methods

Participating Hospitals

Six Canadian, university-affiliated hospitals participated in the study: five in Quebec and one in Ontario. The research protocol was approved by each institutional review board.

Study Population and Recruitment

From March 6, 2006, to June 25, 2007, all consecutive patients 18 years of age or older admitted on selected units were asked to participate in the study. The selected units were those with a historically high or low incidence of C. difficile infection. We excluded patients who had hemodynamic instability, who were receiving palliative care, who had neutropenia (an absolute neutrophil count ≤1000 per cubic millimeter), or who were unable to participate in the informed-consent process on their own behalf or represented by a surrogate. All participants gave written informed consent.

Study Definitions

C. difficile infection was defined as follows: the presence of diarrhea and a positive C. difficile cytotoxin assay or toxigenic culture, the presence of diarrhea without an alternative explanation and an endoscopic diagnosis of pseudomembranes, or a pathological diagnosis of C. difficile infection. Diarrhea was defined as three loose stools within at least one 24-hour period. Asymptomatic C. difficile colonization was defined as a positive stool culture for C. difficile in the absence of diarrhea.

Colonization or infection was considered to be health care–associated if symptoms began 72 hours or more after admission, if C. difficile infection was diagnosed within 4 weeks after discharge from any health care institution, or if the person with colonization or infection was a health care worker in contact with patients.

Recurrence was defined as a second episode of C. difficile infection within 60 days after the first episode. An episode of C. difficile infection occurring more than 60 days after the first event was considered a new episode.

Clinical Data

Data on demographic information, known risk factors, and potential confounding factors were collected. In particular, information about the use of various medications during the 8 weeks before, as well as during, hospitalization was collected for all patients. For patients in whom health care–associated C. difficile infection or colonization developed, the specific start and stop dates of these medications were also recorded to assess whether this exposure occurred before the event of either health care–associated C. difficile infection or colo-
nization. Patients were followed daily until ward discharge, death, or withdrawal from the study. Patients were contacted 60 days after discharge to determine whether diarrhea had developed in the interim.

Outcomes studied were recurrence of \( C. \) difficile infection, death, need for colectomy, and need for intensive care owing to health care–associated \( C. \) difficile infection. For any death, two physicians judged independently whether health care–associated \( C. \) difficile infection was an attributable cause, a contributory cause, or unrelated to the cause of death. In the case of a disagreement, a consensus was reached.

**CLINICAL SAMPLES**
Rectal swabs or stool samples for toxigenic \( C. \) difficile culture were obtained on admission, weekly during hospitalization, at the onset of diarrhea (if applicable), and at discharge. A rectal swab was obtained if a stool sample could not be procured on the scheduled day of sampling. Serum samples were obtained on admission for measurement of antibody levels.

**LABORATORY ASSAYS**
Toxigenic \( C. \) difficile culture was performed on stool samples or rectal swabs with the use of standard methods.\(^{18}\) PFGE and assays to detect the binary toxin and the \( tcdC \Delta 117 \) deletion were performed on \( C. \) difficile isolates. Detection of antibodies against toxins A and B was performed with the use of purified recombinant fragments containing the carboxy terminal of toxin A (residues 1753 to 2681) and toxin B (residues 1751 to 2366) of \( C. \) difficile.\(^{19}\) An enzyme-linked immunosorbent assay similar to that of Warny and colleagues was used.\(^{20}\) For additional details, see the Laboratory Assays section in the Supplementary Appendix (available with the full text of this article at NEJM.org).

**STATISTICAL ANALYSIS**
Epidemiologic and molecular data were collected and interpreted independently. Eligible patients who decided not to participate and those who did participate were compared with respect to mean age and sex.

Participants were categorized into four groups, according to status with respect to \( C. \) difficile infection or colonization and origin of acquisition: patients with health care–associated \( C. \) difficile infection, patients with health care–associated \( C. \) difficile colonization, those with colonization at admission, and those with neither health care–associated \( C. \) difficile infection nor colonization. The cumulative incidences of health care–associated \( C. \) difficile infection and colonization were calculated with the use of competing-risks analysis.\(^{21}\) The SAS software package, version 9.2 (SAS Institute), was used for all statistical analyses.

To study the association between potential risk factors and health care–associated \( C. \) difficile infection and colonization, we selected control patients admitted to the study units. The control group for health care–associated \( C. \) difficile infection comprised both patients with health care–associated \( C. \) difficile colonization only and patients without colonization or infection. Controls for \( C. \) difficile colonization had neither \( C. \) difficile infection nor colonization.

To ensure that case patients and control patients had similar risks of exposure to \( C. \) difficile, a frequency-matching approach was used that linked all affected patients and controls within each stratum defined by a combination of values for hospital and length of stay. The length of stay was defined as the time from admission until diagnosis of \( C. \) difficile infection or colonization (for infected and colonized patients, respectively) or discharge (for controls).

Univariate and multivariate conditional logistic-regression models were used, with health care–associated \( C. \) difficile infection and colonization as the outcomes. Analyses included all controls who could be matched to at least one case patient; patients without \( C. \) difficile infection could serve as controls for more than one patient with health care–associated \( C. \) difficile infection.

In analyses of health care–associated \( C. \) difficile infection, 9 patients with infection were excluded because there were no controls with the same length of stay in the same hospital, and another 4 were excluded because they had missing covariate information; the remaining 104 patients with health care–associated \( C. \) difficile infection were each matched to between 1 and 123 controls with the same length of stay in the same hospital. In analyses of health care–associated \( C. \) difficile colonization, 7 patients with colonization were excluded because there were no controls with the same length of stay in the same hospital, as well
as 1 patient with missing covariate information; the remaining 115 case patients were matched to between 1 and 80 controls each.

The prespecified covariates included age, sex, score on the Charlson comorbidity index,\textsuperscript{22} status with respect to previous hospitalization, serologic data, and status with respect to medication use in the 8 weeks before hospitalization or before \textit{C. difficile} infection or colonization. Medication use was treated as a dichotomous covariate rather than as time dependent because we had data on dates of medication use only for patients in whom health care–associated \textit{C. difficile} infection or colonization developed. The models included antibiotic use as a single summary variable indicating exposure to any antibiotic.

An unconditional logistic-regression model with adjustment for length of stay and hospital was used to determine the association between risk factors and health care–associated \textit{C. difficile} infection among patients with positive cultures for \textit{C. difficile}. This strategy was chosen because of the limited numbers of study participants and matched case–control pairs among patients with positive cultures for \textit{C. difficile}, whether they had infection or just colonization. PDPGE type, \textit{tdcC} \Delta117 deletion status, and presence or absence of binary toxin were used as the genomic covariates. In this analysis, three patients with infection and one patient with colonization were excluded on the basis of missing covariate information.

### RESULTS

#### STUDY UNITS

Each hospital had between 1 and 4 study units, for a total of 14 units: 8 general medicine, 5 general surgery, and 1 hepatobiliary. Each unit had between 23 and 49 beds. The number of admissions ranged from 549 to 1816 per year.

#### STUDY PATIENTS

A total of 12,304 patients were approached about participation, of whom 2802 were not eligible. Among the 9502 eligible patients, 5422 (57.1\%) agreed to participate in the study. Among patients who became infected with \textit{C. difficile} during the study, 75 were excluded because of the development of \textit{C. difficile} infection within 72 hours after admission or within 60 days before admission or because of colonization detected on admission followed by development of infection. Six other patients with a history of \textit{C. difficile} infection in the 60 days before admission were excluded: 3 had asymptomatic colonization and 3 had neither infection nor colonization at the time of admission. A total of 1198 of the 5422 patients (22.1\%) could not be evaluated because of incomplete stool or rectal samples. In all, 4143 patients (76.4\%) had complete clinical assessments and stool or rectal samples and were included in the analysis (Fig. 1).

Eligible nonparticipants were younger than participants, by 0.77 years (95\% confidence interval [CI], –1.45 to –0.09), and were more likely to be women (difference of 2.6 percentage points; 95\% CI, 0.6 to 4.7\%). Participants who could not be evaluated were older than those who could be evaluated, by 1.6 years (95\% CI, 0.6 to 2.6\%), and were more likely to be men (difference of 1.1 percentage points; 95\% CI, –2.2 to 4.4%).

#### INCIDENCE AND OUTCOMES

Of the 4143 patients who could be evaluated, 184 (4.4\%) had asymptomatic colonization at the time of unit admission, 117 (2.8\%) had health care–associated \textit{C. difficile} infection, and 123 (3.0\%) had health care–associated \textit{C. difficile} colonization (Fig. 1). The incidences of health care–associated \textit{C. difficile} infection and colonization were 28.1 cases per 10,000 patient-days and 29.5 per 10,000 patient-days, respectively. Table 1 shows the baseline characteristics of the patients. As compared with the other groups, patients with health care–associated \textit{C. difficile} infection tended to be older and were more likely to have been receiving antibiotics or proton-pump inhibitors within 8 weeks before or during hospitalization.

Figure 2 shows the times to health care–associated \textit{C. difficile} infection and colonization. The time to health care–associated \textit{C. difficile} infection was twice that of health care–associated \textit{C. difficile} colonization. For example, colonization had occurred in 2.5\% of patients at 7 days, whereas infection had occurred in 2.5\% of patients at 14 days.

Among the 117 patients with health care–associated \textit{C. difficile} infection, 14 deaths occurred within 60 days after the diagnosis of \textit{C. difficile} infection, for a crude mortality rate of 12.0\%. \textit{C. difficile} infection was the attributable cause of death in 2 of the 117 patients (1.7\%), contributed to the cause of death in 6 patients (5.1\%), and was unrelated to the cause of death in the remaining 6 patients (5.1\%). Because of \textit{C. difficile} infection, 1 of the 117 patients (0.8\%) required intensive care. None of the patients required colectomy. Twenty-nine of the 117 infected patients (24.8\%) had a
recurrence, with 21 (17.9%) having one recurrence, 6 (5.1%) having two recurrences, and 2 (1.7%) having more than two recurrences.

Among the 60 excluded patients who became infected with \textit{C. difficile} within 72 hours after admission, 42 (70.0%) had been hospitalized during the previous 3-month period, 2 (3.3%) had been admitted from a rehabilitation center and long-term care, and 16 (26.7%) had either never been hospitalized or had been hospitalized more than 12 months previously.

**C. difficile isolates**

Laboratory analyses were performed on 383 available isolates. Patients with health care–associated \textit{C. difficile} infection were more likely to be infected with NAP1 strains, strains that contained the binary toxin, or strains of the \textit{tcdC} \textit{Δ117} genotype than were patients with \textit{C. difficile} colonization (Table 1). Stool samples obtained from 3 patients with \textit{C. difficile} infection had nontoxigenic strains but had positive results on a direct stool cytotoxin assay sent in parallel for routine testing. Isolates were available for 119 (96.7%) of 123 patients with health care–associated \textit{C. difficile} colonization, 30 (25.2%) of whom had nontoxigenic strains (neither NAP1 nor NAP2).

**Risk factors for health care–associated \textit{C. difficile} infection or colonization**

Older age, use of antibiotics, and use of proton-pump inhibitors were all significant risk factors for health care–associated \textit{C. difficile} infection (Table 2). Hospitalization in the previous 2 months;
The use of chemotherapy, proton-pump inhibitors, or H₂ blockers; and the presence of antibodies against toxin B were significant risk factors for health care–associated C. difficile colonization. Among patients with positive cultures for C. difficile, patients with health care–associated C. difficile infection were more likely than those with health care–associated C. difficile colonization to be older,
to have used antibiotics or proton-pump inhibitors, and to have the NAP1 strain (Table 3). Two other multivariate logistic-regression models were studied that included the same variables except that tcdC Δ117 genotype or binary toxin was included instead of NAP1 strain, but the model with NAP1 as the genomic variable provided a better fit with the data and had a more favorable discriminatory value (i.e., a higher concordance [C] statistic) (data not shown).

**DISCUSSION**

Health care–associated *C. difficile* infection and health care–associated *C. difficile* colonization were differentially associated with defined host and pathogen variables. Older age, use of antibiotics, and use of proton-pump inhibitors were significantly associated with health care–associated *C. difficile* infection, whereas previous hospitalization, chemotherapy, use of proton-pump inhibitors or H$_2$ blockers, and antibodies against toxin B were associated with health care–associated *C. difficile* colonization. Patients with health care–associated *C. difficile* infection were more likely to be infected with the NAP1 strain than were patients with health care–associated *C. difficile* colonization.

Our study not only confirms the finding in other studies that older age is a risk factor for health care–associated *C. difficile* infection but also provides a quantitative estimate of the association. For every additional year of age after age 18, the risk of health care–associated *C. difficile* infection increases by approximately 2%. Use of antibiotics or proton-pump inhibitors was also found to be a risk factor for health care–associated *C. difficile* infection. The incidence of *C. difficile* infection might be decreased if use of these medications were reduced. We measured levels of antibodies against toxins A and B at the time of admission and did not find a significant association between these levels and subsequent health care–associated *C. difficile* infection; neither did Kyne and colleagues, although they also measured antibody levels serially during hospitalization and found that patients with higher IgG antibody levels against toxin A after the acquisition of *C. difficile* are more likely to become asymptomatic carriers and less likely to become infected with *C. difficile* than are patients with lower IgG antibody levels. Other studies have examined levels of antibodies against toxin A within a certain period before or after infection and colonization but not at the time of admission, and therefore they are not comparable to our study.

The factors we found to be associated with health care–associated *C. difficile* colonization were previous hospitalization; use of chemotherapy, proton-pump inhibitors, or H$_2$ blockers; and the presence of antibodies against toxin B at the time of admission. Previous hospitalization suggests previous exposure to *C. difficile* and possibly the subsequent development of immunity. Chemotherapy, proton-pump inhibitors, and H$_2$ blockers may disrupt the bowel flora and allow for *C. difficile* colonization. Antibodies against toxin B may permit colonization by *C. difficile* but prevent infection. Antibodies against toxin A were not significantly associated with health care–associated *C. difficile* colonization. This result is supported by a study of *C. difficile* infection showing that toxin B is essential, and toxin A is less important, for virulence; other studies have shown that *C. difficile* strains that are negative for toxin A but positive for toxin B can cause disease. In addition, low levels of serum antibodies against the receptor-binding epitope domain of toxin B have been significantly associated with recurrent disease. Hence, antibodies against toxin B may have protective effects and may be a potential target for vaccine development.

Bacterial factors also affected outcomes in our study. Patients with health care–associated *C. difficile* infection were more likely to have the NAP1 strain than were patients with health care–associ-
ated \textit{C. difficile} colonization only. We found that the NAP1 strain was an independent risk factor for health care–associated \textit{C. difficile} infection after taking potential confounders into account. The NAP1 strain is postulated to be more virulent than others because of a deletion in the \textit{tcdC} gene leading to increased toxin A and B production.\textsuperscript{29} Colonization with a non-NAP1 strain may result in the development of antibodies against toxin B that then confer protection against acquisition of the NAP1 strain. Two studies have shown that colonization with nontoxigenic or toxigenic \textit{C. difficile} strains is associated with a decreased risk of \textit{C. difficile} infection, but the effect of antibodies was not studied.\textsuperscript{8,30}

The incidence of health care–associated \textit{C. difficile} colonization was approximately 29 cases per 10,000 patient-days in our study, which was similar to the incidence of health care–associated \textit{C. difficile} infection. As compared with previous studies, our study showed a higher incidence of health care–associated \textit{C. difficile} infection and a lower incidence of health care–associated \textit{C. difficile} colonization; therefore, the ratio of infection to colonization was higher than that in previous studies.\textsuperscript{7,31}

Johnson and colleagues studied 399 patients, of whom 52 (13%) had health care–associated \textit{C. difficile} colonization and 31 (8%) had health care–associated \textit{C. difficile} infection.\textsuperscript{31} One strain accounted for 28% of the isolates. Johnson and

\begin{table}
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\caption{Odds Ratios for Health Care–Associated \textit{Clostridium difficile} Infection and Colonization According to Various Patient and Pathogen Characteristics.\textsuperscript{*}}
\begin{tabular}{|l|c|c|}
\hline
Variable & Health Care–Associated \textit{C. difficile} Infection & Health Care–Associated \textit{C. difficile} Colonization \\
\hline
Age — per increase of 1 yr & 1.02 (1.00–1.04) & 1.00 (0.99–1.02) \\
Score on Charlson comorbidity index — per unit & 1.01 (0.93–1.10) & 1.02 (0.95–1.10) \\
Male sex vs. female sex & 0.98 (0.64–1.49) & 1.11 (0.75–1.64) \\
Hospitalization before current admission & & \\
Never or >12 mo before & Reference & Reference \\
2–12 mo before & 1.25 (0.76–2.07) & 1.19 (0.74–1.90) \\
<2 mo before & 1.61 (0.94–2.75) & 2.18 (1.31–3.61) \\
Colonization with \textit{C. difficile} ≤3 days before health care–associated infection & 1.32 (0.57–3.02) & NA \\
Use of nasogastric tube\textsuperscript{†} & 1.28 (0.56–2.92) & 0.81 (0.37–1.73) \\
Medication use\textsuperscript{†} & & \\
Antibiotic & 5.25 (2.15–12.82) & 1.04 (0.61–1.78) \\
Chemotherapy & 1.33 (0.49–3.65) & 2.37 (1.09–5.14) \\
Proton-pump inhibitor & 2.64 (1.71–4.09) & 1.71 (1.15–2.53) \\
\textit{H}_2\textsuperscript{blocker} & 0.98 (0.55–1.73) & 2.14 (1.24–3.70) \\
Glucocorticoid & 0.97 (0.48–1.97) & 1.33 (0.72–2.45) \\
NSAID & 0.85 (0.55–1.30) & 1.21 (0.79–1.84) \\
Serologic analysis & & \\
Positive for antibody against toxin A vs. negative & 0.72 (0.41–1.29) & 1.02 (0.62–1.67) \\
Positive for antibody against toxin B vs. negative & 1.27 (0.80–2.02) & 1.75 (1.15–2.66) \\
\hline
\end{tabular}
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\textsuperscript{*} Odds ratios were calculated with the use of conditional logistic-regression analysis of patients with health care–associated \textit{C. difficile} infection or colonization as compared with matched controls. There were 104 patients with infection and 1989 controls (for a total of 2093 patients) and 115 patients with colonization and 1425 controls (for a total of 1540 patients). For analysis of infection, controls were selected from patients admitted to the study units who had colonization only or neither colonization nor infection; for analysis of colonization, controls were selected from patients who had neither infection nor colonization. NA denotes not applicable.

\textsuperscript{†} Medication use and nasogastric-tube use were defined as use within 8 weeks before hospitalization or during hospitalization but before health care–associated \textit{C. difficile} infection or colonization.
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colleagues studied 282 patients, of whom 51 (18%) had health care–associated C. difficile colonization and 9 (3%) had health care–associated C. difficile infection, with either restriction-endonuclease (REA) type B or REA type B2 accounting for all cases. 7

The differences between these two studies and ours can be explained by several factors. The NAP1 strain was predominant in our study, accounting for approximately 63% of isolates among patients with health care–associated C. difficile infection. The NAP1 strain may be more likely than other strains to cause symptomatic disease. Also, the incidence of health care–associated C. difficile colonization in our study is likely to be underestimated because the proportion of incomplete stool or rectal samples may have been higher among patients with asymptomatic health care–associated C. difficile colonization than among those with symptomatic infection. Since we did not perform stool-specimen culture for asymptomatic patients at 60 days after discharge, we may have underestimated the incidence of health care–associated C. difficile colonization relative to infection. Finally, admission criteria and case severity may have differed substantially between our study and the prior studies.

The time to health care–associated C. difficile infection was twice the time to health care–associated C. difficile colonization. A possible explanation is that both toxigenic and nontoxigenic strains colonize patients. Many of the toxigenic strains do
not cause C. difficile infection because the patient has an appropriate anamnestic antibody response. Therefore, for a given C. difficile exposure, it is likely that colonization will result rather than infection.

Our study has several limitations. First, the participation rate of 57% was lower than anticipated, and there was a large number of patients who could not be evaluated because of incomplete laboratory samples. The patients with and those without data included in the analysis differed significantly in age; however, the difference (1.6 years) was small and of minimal clinical importance. The absence of clinically significant differences in baseline characteristics between participants and nonparticipants suggests that other confounding factors were also distributed evenly between the two groups, and no major bias was introduced. Second, we did not perform cultures on environmental samples or skin samples from the hands of personnel — two potential sources of health care–associated C. difficile infection and colonization in patients. Finally, our findings are limited to hospitalized patients and may not be applicable to patients with community-associated C. difficile infection.

In conclusion, our study shows differential effects of age, medication use, and host immunity and pathogen variables on health care–associated C. difficile infection and health care–associated C. difficile colonization. The findings add to the understanding of C. difficile infection and colonization and have implications for prevention and therapy. Supported by the Consortium de Recherche sur le Clostridium difficile; the consortium consists of the following partners: Fonds de la Recherche en Santé du Québec, Canadian Institutes of Health Research, Ministère de la Santé et des Services Sociaux du Québec, Institut National de Santé Publique du Québec, Health Canada, Centre Hospitalier de l’Université de Montréal, McGill University Health Centre, CHU de Québec, and CHU de Sherbrooke.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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