Published in final edited form as:

Gut. 2012 November ; 61(11): 1538–1542. doi:10.1136/gutjnl-2011-301378.

Statin use and the risk of *Clostridium difficile* in academic medical centres

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Abstract

Objectives—To estimate the possible relationship between statin use and the risk of healthcare facility onset *Clostridium difficile*.

Methods—Patients over 18 years of age admitted to hospitals contributing data to the University HealthSystem Consortium between 2002 and 2009 were eligible. Patients with the ICD-9-CM code 008.45 who received a minimum 3-day course of either metronidazole or oral vancomycin on/after day 5 of admission were considered incident cases of *C difficile* infection. 31 472 incident cases of *C difficile* infection were identified and matched to five controls, on hospital, year/quarter of admission date, and age ± 10 years (N=78 096). Patients who were administered one drug in the statin class (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin) before the index date were considered to be exposed. Conditional logistic regression modelling provided adjusted odds ratios and 95% CI.

Results—Compared with non-users, users of any drug within the statin class were 0.78 times less likely to develop *C difficile* infection in the hospital (95% CI 0.75 to 0.81) adjusting for potential confounders. Differences in estimates for specific statins were minimal. Niacin, fibrates and selective cholesterol absorption inhibitors showed no association with the risk of *C difficile* infection.

Conclusions—Our data were consistent with a growing body of literature demonstrating a reduced risk of infections with statin use. Statins' pleiotropic properties may provide protection against *C difficile* infection.

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Contributors CAMF and KLL were responsible for the study design, data analysis and interpretation. AP and RP were responsible for the study design, data acquisition and interpretation. GG was responsible for data interpretation.

Competing interests RP has received grant funding from Merck, Astellas and Cubist Pharmaceuticals. KLL has consulted for OrthoMcNiell Janssen Scientific Affairs on pain management in nursing homes. The other authors declare they have no competing interests.

Ethics approval Ethics approval was provided by the Virginia Commonwealth University Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Clostridium difficile is a spore-forming, anaerobic, Gram-positive bacterium that is thought to be responsible for approximately 20% of cases of hospital-acquired diarrhoea.¹ Recent estimates indicate more than 250 000 hospitalisations associated with *C difficile* infection,² which appears to be increasing.³ In the USA, mortality rates due to *C difficile* infection have also increased, very likely caused by a new more virulent strain of *C difficile*.⁴ The cost of managing *C difficile* infection is not trivial, exceeding US\$3.2 billion.^{5,6}

In addition to age⁷ and disease severity,⁸ risk factors for *C difficile* infection include the use of antibiotics⁹ and gastric acid suppressants.¹⁰ The relationship between statin use and healthcare facility (HCF) onset *C difficile* infection has previously been hypothesised; however, this relationship has not previously been explored.¹¹ In general, statins have been associated with a reduced risk of infections.¹² The prophylactic nature of statins in these infections is possibly due to the myriad of pleiotropic effects of these drugs.¹³ There is a biological basis for belief in these effects, stemming from mechanisms involving immunomodulatory and cell signalling pathways.¹⁴ Briefly, statins are hypothesised to reduce inflammation in endothelial cells.¹⁵ The reduced inflammation could either reduce the risk of acquiring *C difficile* infection, or reduce the severity of *C difficile* infection. Other epidemiological studies¹⁶ have previously found a reduced risk of *C difficile* infection in patients taking statins.

In the USA, statin use has increased significantly, with 24 million Americans (35.9% of those with high low-density lipoprotein cholesterol levels) taking statins in 2003–4 compared with 12.5 million (19.6% of those with high low-density lipoprotein cholesterol levels) taking statins in 1999–2000.¹⁷ As a result of the increase in the prevalence of statin use, it is especially important to understand what other effects may be perpetuated beyond their intended cholesterol-lowering purpose. The extent and magnitude of the pleiotropic nature of statins in infections is just beginning to come into focus. Therefore, evaluating the indirect effects of statins in conjunction with specific infections, such as *C difficile* infection, is warranted.

The purpose of this study was to determine the extent to which statin use was associated with a decreased risk of HCF-onset *C difficile* infection.

METHODS

Setting and participants

We designed a matched case–control study using data from the University HealthSystem Consortium (UHC). The UHC is composed of 107 academic medical centres and 234 of their associated hospitals, representing approximately 90% of the USA's non-profit academic medical centres.¹⁸ A subset of UHC hospitals participate in the clinical resource manager that served as the data source; it contains uniform billing (UB-92) data, and inpatient medication use from charge transaction masters and billing files as well as information on patient demographics such as age, race and gender, and also includes hospital-level information such as the number of beds. Geographically distributed throughout the USA, the UHC member hospitals vary in bed size (mean 533; SD 190), discharges (mean 23 981, SD 9014), patient days (mean 134 454, SD 52 639) and lengths of stay (mean 5.58, SD 0.54) for 2002–9.

The source population included patients over 18 years of age, admitted to a hospital that contributes information to the UHC database during the study period (2002 to second quarter 2009). The exclusion of patients with conditions that contraindicated statin use was considered, but it was determined that most patients could safely take at least one drug belonging to the statin class, even if certain specific statins were not safe for that patient.

HCF-onset *C difficile* infection cases were defined using a validated algorithm¹⁷¹⁹²⁰ commonly used for surveillance.²¹ Briefly, potential cases were defined as a hospital inpatient stay with a primary International Classification of Disease version 9-CM (ICD-9-CM) code of 008.45. To determine incident *C difficile* infection during the hospital stay, we took into consideration the initiation of medications used for the treatment of *C difficile* infection. Patients with a primary ICD-9-CM code of 008.45 and who initiated either metronidazole or oral vancomycin for the treatment of *C difficile* infection and received at least 3 days on/after day 5 of admission were considered as cases. Controls were required to have been in the hospital for a minimum length of stay of at least 8 days, to eliminate bias as a result of less time spent in the hospital. This case definition has good sensitivity (71%), excellent specificity (100%) and a positive predictive value of 80%.¹⁷ Using this definition, we identified 24 551 cases. Cases were matched to controls on age (within 10 years), hospital, and year/quarter. We matched on hospital to reduce confounding by hospital size, geographical location, case mix index and other organisational factors that may have distorted the relationship under study. We matched on year/quarter within hospital to account for the seasonality of *C difficile* infection. Over 99% of cases were matched to five controls.

Exposure status

The UHC database includes detailed information regarding every medication administered in the hospital setting for which charges were generated. The UHC resources have previously been used for studies ranging from radiation exposure²² to inpatient mortality.²³ Data fields include the medication name, date of initiation, date of discontinuation and days of therapy. The start date for each medication represents the first day the particular medication was administered and the stop date represents the last day each medication was administered. Days of therapy are calculated for each medication as the total number of days charges existed for each particular medication within the hospital stay. We assumed that the days of therapy represented continuous use; patient-level charge data were not available. Statin users who were administered one medication in the statin class (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin) before the index date (post-admission date of developing *C difficile* infection or 5 days post admission for controls) were considered exposed. Patients who received a drug combination that included a statin (eg, atorvastatin plus amlodipine, simvastatin plus ezetimibe) were also considered statin users. Participants who were prescribed a statin within 48 h of admission to the hospital were assumed to be long-term users of statins, and this assumption is supported by previously conducted work.²⁴ To evaluate the possibility that the indication for the medications (eg, cholesterol lowering) and not statins were driving the risk of *C difficile* infection, we also created dummy variables for selective cholesterol absorption inhibitors, resins, fibrates and niacin. The use of multiple cholesterol-lowering medications was considered separately from cholesterol-lowering drugs provided as monotherapy. We were thus able to estimate the effect of monotherapy of particular statins and other cholesterol-lowering medications relative to non-users of any cholesterol-lowering medication.

Potential confounders

A number of patient-level confounders were considered. Increasing age is known to be associated with an increase in *C difficile* diagnoses, and advanced age is also associated with an increase in the number of statin prescriptions filled.²⁵ Race²⁶ and gender²⁷ are also both known to influence the use of statins. In previous studies, men have been more likely to receive a prescription for a statin relative to women for similar indications. Racial disparities are well documented in the prescription of statins, and the drugs are commonly underprescribed to black patients.²⁴ We also considered clinical complexity as a potential confounder. We calculated the Charlson comorbidity index, a measure of the burden of

coexistent disease that weights and scores the impact of 17 chronic diseases to create an overall score.²⁸ This measure has been repeatedly validated in large populations.^{29,30}

Analytical approach

Descriptive statistics were used to explore the composition and medication use of cases and controls. To take into consideration the variable matched study design, conditional logistic regression modelling provided crude OR, adjusted OR and 95% CI. We used a forward selection process, but not computer driven, adding potential confounders to the model one at a time. We retained variables that changed the estimate of effect by 10% or more, while being cautious not to include collinear variables. We also forced antibiotic use and proton pump inhibitor use into the models because they are important risk factors for *C difficile* infection.^{9,10}

The Institutional Review Board of Virginia Commonwealth University fully approved the use of this database and this study protocol.

RESULTS

Table 1 shows the characteristics of cases and their matched controls. Over three-quarters were non-Hispanic white, approximately half were between the ages of 35 and 64 years and approximately half were men. The use of antibiotics (other than vancomycin or metronidazole) and gastric acid suppressants was higher among cases than controls. The distribution of the comorbidity index varied by case status; cases appeared to have slightly more coexistent disease relative to controls.

Overall, one-fifth of patients used statins. Atorvastatin was used by 7.3% of cases and 9.2% of controls, and simvastatin had a similar usage pattern. Other statins were used less frequently. The use of combination drugs containing a statin was limited among both cases and controls. For cholesterol-lowering drugs that are not considered statins, 3.2% of cases and controls used selective cholesterol absorption inhibitors. In addition, 1.0% or less of cases and controls used resins or niacin. Overall, the use of cholesterol-lowering medications was evenly distributed among the case and control populations.

Table 2 shows the association between overall statin use and individual drugs within the statin class and *C difficile* infection. Compared with non-users of any cholesterol-lowering medication, users of any drug within the statin class were less likely to develop *C difficile* infection while in the hospital (adjusted OR 0.78; 95% CI 0.76 to 0.84). Each statin drug individually also had a protective effect on the risk of HCF-onset *C difficile* infection, and the degree of protection was very similar among individual statins.

Table 3 shows the association between other cholesterol-lowering medications and HCF-onset *C difficile* infection.

Patients taking niacin, ezetimibe or fibrates did not have an increased or decreased risk of being diagnosed with *C difficile* infection compared with patients not taking any cholesterol-lowering medication. After adjusting for potential confounders, patients taking resins were 3.56 times as likely to develop a *C difficile* infection in the hospital (95% CI 2.72 to 4.65) than patients not taking any cholesterol-lowering medication.

DISCUSSION

Using a previously validated definition of HCF-onset *C difficile* infection,¹⁷ we found that the use of statins decreases the risk of HCF-onset *C difficile* infection. This is consistent

with the outcomes of other studies investigating correlations between statins and infections. The large sample size enabled by the UHC data permitted medication-specific estimates, and is a key strength of this study. The protective association held when looking at individual statin formulations, not just the overall statin class. No association between non-statin cholesterol-lowering drugs was observed, further strengthening the support for our hypothesis. While our study suggests that statin use decreases the risk of HCF-onset *C difficile* infection, a number of alternative explanations must be considered.

Residual confounding could have distorted our estimates, although it is unclear what variables might have introduced the level of confounding required to explain the strength of these findings. While matching was based on age, hospital and year of admission, information was not available on other characteristics of the population, such as socioeconomic status, which may have skewed our effect measures. Administrative claims data are based on hospital charges, and hospital charges are driven by what is reimbursable for insurance purposes; laboratory data and other patient-level records were not available. In addition, dosing information was not available, and as such we were unable to perform evaluations of possible dose-response relationships. Another potential limitation is the lack of information available on the patient location within a given hospital (eg, specific floor or ward). An important risk factor for *C difficile* infection, like other infectious diseases, is exposure to and transmission from *C difficile* infection patients or carriers.³¹ Unfortunately, the database does not contain information as to ward or patient room sharing, so we are unable to infer potential *C difficile* infection transmission from these sources. We did, however, match on hospital and year/quarter and adjust for hospital rate of *C difficile* infection. In addition, previous gastrointestinal surgery was not considered a potential confounder. However, the authors believe that surgical procedures would not have significantly confounded the association due to the lack of papers citing gastrointestinal surgery as a potential risk factor.

It is possible that preventive medications such as statins may have been discontinued on admission to the hospital. Indeed, statin use in our study was lower than in the typical US population. Nevertheless, prevalence estimates of statin use based on UHC data are comparable with statin use in other hospitalised populations.³² In this population, monotherapy of statins was used by 16.4% of cases and 20.3% of controls compared with 23% usage in previous studies.³² One possible explanation for the lower use of statins in hospitalised populations is that some drugs may be discontinued when patients are admitted to hospital. However, if this misclassification occurred, it would have diluted the estimate of effect.

Statins have been cited to have multiple protective effects including reducing the risk of cataract,³³ Alzheimer's disease,³⁴ improving outcomes in community acquired pneumonia,³⁵ reducing the risk of renal cell carcinoma,³⁶ and particularly relevantly, reducing mortality due to sepsis and other infections.³⁷ Recently, the JUPITER trial demonstrated the role of statins for primary prevention in apparently healthy men and women.³⁸ All of these effects of statins may be considered pleiotropic side effects of the drugs, and many are due to the anti-inflammatory and immunomodulatory properties of the drugs.¹⁵³⁹ One of the mechanisms proposed for statins to affect the immune system is by increasing the phagocyte's ability to create extracellular traps.³⁹ The multitude of observed pleiotropic side effects contributes to the possibility that more unknown effects of statins are present and have yet to be explored. Few studies have been adequately powered to provide individual estimates of effect for statins and other cholesterol-lowering medications due to small sample size and the low frequency of non-statin medication use. In one study exploring the association between statin use and colorectal cancer,⁴⁰ a possible protective effect of statins on colorectal cancer was observed; however, trends towards risk reductions were also

observed for non-statin cholesterol-lowering drugs. How elevated cholesterol may create adverse conditions for *C difficile* infection remains unclear.

While statins have been shown to reduce the risk of a number of different infections^{1241–44} and other morbidities that could potentially involve inflammatory pathways, other studies and reviews suggest that this observation could be due to a healthy user effect.¹² However, without a randomised controlled trial, an observational study will not be able to eliminate all potential elements that could be contributing to the healthy user bias.

Unexpectedly, we found that resins (bile acid sequestrants) were positively associated with the development of HCF-onset *C difficile* infection. Resins, including cholestyramine, colestipol and colesevelam, have previously been recommended in combination with statins to reduce lipid levels further.⁴⁵ Notably, resin users had more comorbid conditions (indicated by a Charlson score of 4 or higher) than non-resin-taking participants. To explain this result, we also considered (and ruled out) confounding due to the diagnosis of pancreatitis, bile obstruction, or liver jaundice. We were unable to disentangle whether confounding by some unmeasured factor remained or if physicians initiated resins to deal with emerging symptoms associated with *C difficile* infection. Resins are used in the treatment of diarrhoea and irritable bowel disease. These uses could lead to a possible protopathic bias, or confounding by indication. These results showing increased risk among resin users warrant further investigation, as findings could be clinically meaningful for patients at high risk of *C difficile* infection.

To the best of our knowledge, this study is the first to consider the role of statins in the risk of hospital-acquired *C difficile* infection; however, other studies have considered the impact of statins on the outcomes of other infectious diseases.⁴⁴⁴⁵ Our findings are not generalisable to those with community-associated *C difficile* infection, or patients outside of academic health centres. However, our results are consistent with a recent study demonstrating the protective effect of statins for community-associated *C difficile* infection.¹⁶ The large size of our study is a strength, as we were able to analyse individual statins and other drugs used in the treatment of hypercholesterolaemia. However, we were unable to evaluate the role of the length of statin therapy on the development on *C difficile* infection. In summary, statins, but not other cholesterol-lowering medications, are associated with a decreased risk of HCF-onset *C difficile* infection. No differences were observed by individual statin medication. This study adds to the accumulating evidence of the unintended beneficial effects of statins on infections. However, only a randomised controlled clinical trial can determine the causal role of statins in preventing infections.

Acknowledgments

The authors would like to acknowledge Sofia Medvedev and Sam Hohmann for their aid in obtaining access to the data.

Funding This study was supported in part by grant number UL1RR031990 and by grant number K08HS018578 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the agency for Healthcare Research and Quality. Neither funding source was involved in any part of the study.

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Significance of this study

What is already known about this subject?

- ▶ Many patients take statin medications.
- ▶ *C difficile* is an important hospital-acquired infection with both individual and organisational implications.
- ▶ Many risk factors for *C difficile* exist including antibiotic use.

What are the new findings?

- ▶ Statin use appears to decrease the risk of the diagnosis of HCF-onset *C difficile*.
- ▶ The reduction of infection risk from statin use may be due to the pleiotropic anti-inflammatory properties of statins.
- ▶ More research needs to be conducted to evaluate further the relationship between statins and *C difficile* infection.

How might it impact on clinical practice in the foreseeable future?

- ▶ Knowledge of potential implications for medication use in the risk of *C difficile*, provided further supporting evidence, could impact clinician determinations of risk for hospital-acquired infections.

Table 1Demographic and clinical characteristics of incident cases of *C difficile* and their matched controls

Patient characteristic	Cases of <i>C difficile</i> infection (n=31 472)	Controls (n=78 096)
Age (years)		
18–34	6.3	4.2
35–64	51.3	50.5
65–74	20.1	21.4
75–84	16.6	18.2
85	5.6	5.7
Men	53.1	51.8
Black, non-Hispanic	18.3	20.4
White, non-Hispanic	67.8	66.7
Hispanic	5.3	4.5
Charlson co-morbidity index		
0	15.1	23.1
1 to 3	53.0	49.3
4 +	31.9	27.7
Medication use		
Statins	17.7	22.1
Non-statin cholesterol-lowering drugs	3.2	3.3
Gastric acid suppressants	61.0	50.3
Antibiotic use	85.8	69.7

Table 2Relationship between statin use and the incidence of *C difficile* infection

	Cases (n=31 472)	Controls (n=78 096)	OR (95% CI)	Adjusted* OR (95% CI)
Any statin	5568	17 218	0.78 (0.75 to 0.84)	0.78 (0.75 to 0.81)
Simvastatin	2528	7743	0.80 (0.76 to 0.84)	0.80 (0.76 to 0.84)
Lovastatin	123	412	0.69 (0.56 to 0.86)	0.72 (0.58 to 0.90)
Atorvastatin	2290	7181	0.78 (0.74 to 0.82)	0.78 (0.74 to 0.82)
Pravastatin	469	1349	0.87 (0.77 to 0.97)	0.86 (0.77 to 0.96)
Non-user	25 904	60 878	1.0	1.0

* The model was built using a 10% change of estimate strategy. Antibiotic use, proton pump inhibitor use, comorbidities, sex, race and ethnicity were tested for inclusion in the model. None were significant confounders; however, antibiotic use and gastric acid suppressant use were retained in the model due to their importance as risk factors for *C difficile* infection.

Table 3Relationship between non-statin cholesterol-lowering drugs and the incidence of *C difficile* infection

	Cases (n=31 472)	Controls (n=78 096)	OR (95% CI)	Adjusted* OR (95% CI)
Selective cholesterol absorption inhibitors	1008	2578	0.84 (0.69 to 1.02)	0.84 (0.69 to 1.02)
Resins	225	174	3.53 (2.76 to 4.52)	3.29 (2.57 to 4.23)
Fibrates	317	949	0.96 (0.79 to 1.16)	0.96 (0.79 to 1.16)
Niacin	62	212	0.68 (0.41 to 1.15)	0.72 (0.42 to 1.22)
Non-user	30 464	75 518	1.0	1.0

* The model was built using a 10% change of estimate strategy. Antibiotic use, proton pump inhibitor use, comorbidities, sex, race and ethnicity were tested for inclusion in the model. None were significant confounders; however, antibiotic use and gastric acid suppressant use were retained in the model due to their importance as risk factors for *C difficile* infection.