Does Doxycycline Protect Against Development of *Clostridium difficile* Infection?

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Background. Receipt of antibiotics is a major risk factor for *Clostridium difficile* infection (CDI). Doxycycline has been associated with a lower risk for CDI than other antibiotics. We investigated whether doxycycline protected against development of CDI in hospitalized patients receiving ceftriaxone, a high-risk antibiotic for CDI.

Methods. We studied adults admitted to an academic county hospital between 1 June 2005 and 31 December 2010 who received ceftriaxone to determine whether the additional receipt of doxycycline decreased the risk of CDI. Patients were followed from first administration of ceftriaxone to occurrence of CDI or administrative closure 30 days later.

Results. Two thousand three hundred five unique patients comprising 2734 hospitalizations were studied. Overall, 43 patients developed CDI within 30 days of ceftriaxone receipt, an incidence of 5.60 cases per 10 000 patient-days. The incidence of CDI was 1.67 cases per 10 000 patient-days in those receiving doxycycline, compared to 8.11 per 10 000 patient-days in those who did not receive doxycycline. In a multivariable model adjusted for age, gender, race, comorbidities, hospital duration, pneumonia diagnosis, surgical admission, and duration of ceftriaxone and other antibiotics, for each day of doxycycline receipt the rate of CDI was 27% lower than a patient who did not receive doxycycline (hazard ratio, 0.73; 95% confidence interval, .56–.96).

Conclusions. In this cohort of patients receiving ceftriaxone, doxycycline was associated with lower risk of CDI. Guidelines recommend this combination as a second-line regimen for some patients with community-acquired pneumonia (CAP). Further clinical studies would help define whether doxycycline-containing regimens should be a preferred therapy for CAP.

Clostridium difficile infection (CDI), a common cause of antibiotic-associated diarrhea, is an important problem in acute care hospitals [1]. Recent studies have shown hospital-acquired CDI rates of 6.5–8.5 per 10 000 patient-days, a 2- to 3-fold increase from older reports [1–3]. In addition, morbidity and mortality associated with CDI have increased, which is likely due to a combination of increased virulence of some strains of *C. difficile* and numerous risk factors among vulnerable hospitalized patients [4–6]. Attributable mortality of hospital-acquired CDI has been estimated at 5.7%–6.9% of cases [2, 7]. A population-based study in the United States reported that mortality due to CDI rose from 5.7 to 23.7 deaths per million people between 1999 and 2004 [4]. Diagnosis of CDI is estimated to raise costs of a hospitalization stay by 54% [8].

Antibiotic exposure is the major risk factor for development of CDI [9–12]. Recent data show that up to 63% of inpatients at academic medical centers in the United States receive at least 1 dose of antibiotics, and up to 7% of people receiving antibiotics develop CDI within 30 days [13–15]. Because inpatients receiving antibiotics are at high risk for the development of CDI, approaches to prevent infection in this population are needed. In addition to parsimonious use of antibiotics, use of lower-risk antibiotics may be one approach, as the risk of CDI varies among the different classes of antibiotics [9, 10, 16, 17]. Doxycycline is one antibiotic

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that may have less potential to cause CDI and possibly protects against infection. Several in vitro studies have shown that therapeutic levels of doxycycline inhibit *C. difficile*, though another study showed evidence of isolates resistant to tetracycline, a closely related antibiotic [18–20]. Tigecycline, a glycylcycline that is a tetracycline derivative, also has activity against *C. difficile* [18, 20]. This antibiotic has been used successfully in a small number of cases of refractory CDI [21]. The in vivo effects of doxycycline on CDI are unclear, though a recent large case-control study examining patients belonging to Kaiser Permanente of Northern California showed that doxycycline conferred protection against CDI in hospitalized patients receiving antibiotics [10]. Several other reports suggest that tetracyclines have little effect or may even predispose to CDI [11, 22].

To address these discrepancies, the goal of this study was to determine whether doxycycline receipt is associated with protection from CDI in a cohort of hospitalized patients receiving ceftriaxone, a high-risk antibiotic for CDI. At our hospital, the main use for doxycycline is in conjunction with ceftriaxone as a first-line therapy for treatment of community acquired pneumonia (CAP) in patients admitted to the ward. Ceftriaxone is used for a number of different indications, including CAP, bone and joint infections, meningitis, endocarditis, and urinary tract infection.

MATERIALS AND METHODS

Study Design and Population

A historical cohort study was performed at San Francisco General Hospital, a 300-bed county hospital, during the period from 1 June 2005 through 31 December 2010. Individual hospitalizations were analyzed, and patients could contribute more than 1 hospitalization to the cohort. The cohort consisted of patients ≥18 years old admitted during the study period who received at least 1 dose of ceftriaxone during their hospitalization. Patients were excluded if they were diagnosed with CDI in the 30 days prior to admission through 2 days after admission, or if they were diagnosed with CDI prior to initiation of ceftriaxone. The University of California, San Francisco Committee on Human Research approved this study.

Predictor and Covariate Measurements

Dates and name of systemic antibiotics received by any route for each patient during hospitalization were collected from a pharmacy database. For the main analysis, antibiotics other than ceftriaxone and doxycycline were grouped together. For the analysis looking by antibiotic class, antibiotics were grouped as follows: aminoglycosides, early-generation cephalosporins (first and second generation), late-generation cephalosporins (third and fourth generation plus aztreonam and excluding ceftriaxone), clindamycin, macrolides, metronidazole, penicillin and penicillin derivatives, β-lactamase inhibitor combinations (majority were piperacillin/tazobactam), fluoroquinolones, trimethoprim/sulfamethoxazole, doxycycline, and other (daptomycin, linezolid, and vancomycin). Carbapenems, mainly ertapenem, were prescribed rarely (~3%) and were combined with piperacillin/tazobactam given similar spectrums of activity. Duration of antibiotic exposure was obtained from start and stop dates. Dosing information and outpatient antibiotic information was not available.

Once the cohort of patients receiving ceftriaxone had been identified, admission and discharge dates associated with the antibiotic receipt were derived from hospital databases. In addition, demographic information, including age, gender, and race, and admitting service were also obtained from these databases. Comorbidities known to be present at the time of hospitalization were quantified with the Charlson comorbidity index, which was derived from the International Statistical Classification of Diseases and Related Health Problems (ICD)–9 codes recorded in electronic hospital databases [23]. Primary diagnosis was available in electronic records only as a free-text field. Pneumonia was assumed if the primary admission diagnosis included the notations "PNA," "pna," "Pna," "pneumonia," "PNEUMONIA," or "Pneumonia."

Outcomes

The outcome of interest was development of CDI within 30 days of ceftriaxone initiation. CDI was defined by a positive stool test for *C. difficile* ordered by the treating team for clinical indications [24]. During this period of time, stool testing was done with an enzyme immunoassay for toxins A and B. Dates of CDI diagnosis were identified through infection control databases. Only the first positive stool test was included. Results of both inpatient and outpatient CDI testing done through the San Francisco Department of Public Health were included. Roughly 60% of inpatients are seen in primary care clinics associated with the San Francisco Department of Public Health, and even more than that are followed in specialty clinics. Patients diagnosed with CDI outside of this system could not be included as cases, as these data were not available.

Data Analysis

A survival analysis with a Cox proportional hazards model was used to estimate the hazard for the development of CDI at 30 days after ceftriaxone administration. Time zero was defined as the first day of ceftriaxone receipt. If ceftriaxone was started within 48 hours after admission, the data were left-truncated because CDI diagnoses within the first 48 hours were excluded. Patients were followed for 30 days following ceftriaxone receipt or until the occurrence of CDI, whichever came first. Fixed predictors entered in the model included age, gender, Charlson comorbidity index, length of stay before

ceftriaxone, surgical admission, admission due to pneumonia, and race. Whether a patient was an inpatient or an outpatient was treated as a time-varying covariate as were antibiotic courses to account for differing durations of therapy. The linearity assumption was checked using squared terms. The proportional hazards assumption was tested using scaled Schoenfeld residuals [25]. Statistical analyses were performed in STATA version 11.2 software (StataCorp LP, College Station, TX), with statistical significance set at ≤0.05 for 2-sided tests.

RESULTS

The cohort consisted of 2734 hospitalizations, contributed by 2305 unique patients. Of these, 1977 patients contributed 1 hospitalization (72% of all hospitalizations studied), 247 patients contributed 2 hospitalizations (9% of total hospitalizations), and 81 patients (3%) contributed 3 or more hospitalizations. Baseline characteristics of the cohort are shown in Table 1. Those receiving doxycycline were older, more likely to have pneumonia on admission, less likely to be admitted to a surgical service, had higher Charlson comorbidity indices, and received shorter courses of additional antibiotics than those who did not receive doxycycline. Duration of ceftriaxone receipt, days before development of CDI, and hospital length of stay was similar between the 2 groups.

Table 1. Characteristics of Patients Receiving Ceftriaxone Classified by Doxycycline Receipt, 1 June 2005 Through 31 December 2010

	No DOXY (n = 1668)	DOXY (n = 1066)
Age, mean (SD), years	52.4 (16.4)	53.9 (15.9)
Male, n (%)	1037 (62)	735 (69)
Race, n (%)		
Nonwhite	1099 (66)	693 (65)
White	569 (34)	373 (35)
Charlson comorbidity index, mean (SD)	2.4 (0.1)	2.7 (0.1)
Pneumonia on admission, n (%)	117 (7)	444 (42)
Surgical admission, n (%)	204 (12)	21 (2)
Hospital days before CRO, median (IQR)	1 (0–1)	0 (0–1)
CRO duration, days, median (IQR)	3 (2–5)	3 (3–5)
Additional antibiotic duration, days, median (IQR)	2 (0–6.5)	0 (0–4)
CDI, n (%)	38 (2)	5 (0.5)
Hospital days before CDI, median (IQR)	7 (4–14)	7 (4–12)
Total length of stay, days, median (IQR)	7 (4–14)	7 (4–12)

Abbreviations: CDI, *C. difficile* infection; CRO, ceftriaxone; DOXY, doxycycline; IQR, interquartile range; SD, standard deviation.

Overall, 43 patients developed CDI within 30 days of admission. There were a total of 76 830.26 days of follow-up for the cohort of hospitalizations, resulting in an incidence rate of 5.60 per 10 000 patient-days. Thirty-nine percent of patients (1066) received doxycycline during hospitalization. Of these, 5 developed CDI, an incidence rate of 1.67 per 10 000 patient-days. Of the patients who did not receive doxycycline, 38 developed CDI within 30 days of admission, an incidence rate of 8.11 per 10 000 patient-days. On an unadjusted analysis (Table 2), white race was associated with a 2.67-fold higher hazard of CDI compared to nonwhite race (95% confidence interval [CI], 1.46–4.89). There was a trend toward a protective effect of male gender, with a hazard for development of CDI 0.57-fold that of females (95% CI, .31–1.03). On a bivariate analysis, age, Charlson index score and surgical admission did not appear to confer increased risk of CDI.

Out of the whole population, 800 (29%) patients received 1 additional class of antibiotics besides ceftriaxone or doxycycline, 449 (16%) received 2 additional classes, 273 (10%) received 3 classes, and 177 (6%) received 4 or more additional classes. On a bivariate analysis, for each day of additional antibiotic receipt, the hazard for development of CDI increased 4%. For each day of doxycycline receipt, there was a 0.67-fold lower unadjusted hazard of developing CDI compared to a patient not receiving doxycycline (95% CI, .48–.90).

On a multivariable analysis, receipt of doxycycline was associated with protection against development of CDI in this cohort of patients receiving ceftriaxone (Table 2). For each additional day that a patient received doxycycline, there was a 27% lower rate of CDI compared to a patient not receiving doxycycline when adjusted for age, gender, race, comorbidities, duration of hospitalization, pneumonia diagnosis, surgical admission, and duration of ceftriaxone and other antibiotics. When treated as a binary time-varying variable, receipt of doxycycline resulted in a hazard ratio (HR) of 0.29 (95% CI, .11–.77). In a patient receiving a 5-day course of doxycycline, the hazard for development of CDI was 0.21-fold that of a patient not receiving doxycycline when adjusted for the other factors in the model (95% CI, .05–.82).

In a model controlling individually for antibiotic classes rather than additional antibiotics being grouped together, the HR for each additional day of doxycycline receipt was 0.74 (95% CI, .55–.98). Approximately 14% of the cohort received ceftriaxone plus a macrolide and 8% received ceftriaxone plus a fluoroquinolone, 2 common therapies for CAP that do not include doxycycline. The HR for development of CDI in a patient receiving a 5-day course of doxycycline plus ceftriaxone compared to a 5-day course of a macrolide plus ceftriaxone was 0.15 (95% CI, .03–.77) and was 0.13 compared to a 5-day course of a fluoroquinolone plus ceftriaxone (95% CI, .03–.62) when adjusted for age, gender, race, comorbidities,

Table 2. Unadjusted and Adjusted Analysis for Risk of *C. difficile* Infection

	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Age, per 1 year	1.01 (.99–1.03)	.18	1.01 (.99–1.03)	.26
Gender				
Female	Ref	…	Ref	…
Male	0.57 (.31–1.03)	.06	0.53 (.29–0.99)	.05
Race				
Nonwhite	Ref	…	Ref	…
White	2.67 (1.46–4.89)	.001	2.75 (1.48–5.11)	.001
Charlson index, per point	1.01 (.92–1.12)	.77	1.04 (.95–1.14)	.39
Admitting service				
Nonsurgical	Ref	…	Ref	…
Surgical	1.81 (.77–4.30)	.18	1.10 (.46–2.64)	.83
Admission diagnosis				
Not pneumonia	Ref	…	Ref	…
Pneumonia	…[a]	…	0.22 (.03–1.69)	.15
Time before CRO, per day	1.02 (1.00–1.04)	.09	0.97 (.93–1.02)	.25
Inpatient status, per day[b]	11.7 (5.25–25.9)	<.001	15.1 (5.73–39.6)	<.001
CRO, per day of use	1.03 (.93–1.13)	.58	0.92 (.84–1.02)	.13
DOXY, per day of use	0.67 (.48–0.90)	.008	0.73 (.56–0.96)	.03
Additional antibiotics, per day of use	1.04 (1.02–1.07)	<.001	0.99 (.96–1.03)	.73

Abbreviations: CI, confidence interval; CRO, ceftriaxone; DOXY, doxycycline; HR, hazard ratio; ref, reference.

[a]Unable to calculate unadjusted HR for pneumonia on admission.

[b]Hospitalization, ceftriaxone, doxycycline, and additional antibiotics were treated as time-varying covariates.

duration of hospitalization, pneumonia diagnosis, surgical admission, and duration of ceftriaxone and other antibiotic classes. Because antibiotic exposure data were not available after discharge and because case identification was incomplete after discharge, a sensitivity analysis looking only at only time of hospitalization with censoring at discharge was performed. Results from this analysis were similar to those examining the 30-day endpoint (data not shown).

Duration of ceftriaxone receipt in this cohort did not lead to increased risk of CDI, nor did duration of additional antibiotics. The strongest predictor of CDI in this model was whether a patient remained in the hospital. On any given day, the hazard of CDI for a hospitalized patient was 15.1-fold higher than for an outpatient. Additional demographic factors significantly associated with risk of CDI included female sex and white race.

CONCLUSIONS

In this cohort of hospitalized patients receiving ceftriaxone, receipt of doxycycline was associated with lower risk for the development of CDI. The American Thoracic Society and Infectious Diseases Society of America guidelines recommend doxycycline plus a β-lactam antibiotic as an alternative to a macrolide or fluoroquinolone-containing regimen for the treatment for CAP [26]. At our hospital, the combination of ceftriaxone and doxycycline is recommended first-line therapy for patients with CAP who are admitted to the ward. Therefore, substantial numbers of inpatients receive this antibiotic combination. It should be noted that although only 42% of patients receiving doxycycline had a primary admission diagnosis of pneumonia, we expect that many more were being treated for CAP with ceftriaxone and doxycycline. This diagnosis is a text entry made by the ward clerk on admission, and thus is insensitive for primary diagnosis and does not capture pneumonia as a secondary diagnosis. The results reported herein suggest that doxycycline ought to be reevaluated as a preferred agent for treatment of appropriate infections, including CAP. With a standard 5-day course of therapy for CAP, receipt of doxycycline plus ceftriaxone versus 5 days of ceftriaxone plus a nondoxycycline antibiotic resulted in a 79% decrease in the relative hazard for CDI. These results are in line with the prior case-control study showing an odds ratio of 0.41 for development of CDI in those receiving doxycycline compared to those not receiving doxycycline when matched for additional antibiotics, time in the hospital, comorbidities, and demographics [10].

Doxycycline is a broad-spectrum antibiotic that inhibits protein synthesis. It has excellent bioavailability, undergoes hepatic metabolism, and is excreted in both the kidneys and the

gut [27]. The most straightforward explanation for why doxycycline may be associated with lower risk of CDI is its in vitro activity against anaerobic bacteria, including *C. difficile* [18–20]. An additional possibility is that, as a protein synthesis inhibitor, doxycycline attenuates *C. difficile* toxin production. Because of its maximal absorption in the upper gastrointestinal tract, it has been posited that doxycycline has minimal effects on gut flora, which might also explain the lower risk for CDI [27]. More work will need to be done to elucidate the exact protective mechanism for this drug.

The incidence rate of CDI in this study was lower than reported in other studies. This may have been due in part to the fact that CDI cases diagnosed outside of the San Francisco Department of Public Health system were missed and that the enzyme immunoassay method being used by the laboratory during the study period has poor sensitivity compared to alternative methods [28]. In addition, the incidence rate did not account for cases diagnosed on admission, before ceftriaxone administration, or recurrences, which also likely decreased the rate.

Although the outcome of CDI may have been missed in some patients and may have accounted for a lower incidence rate, it is likely that the number of missed cases was nondifferential with respect to the exposure to doxycycline. Thus, if the HR estimates were biased due to this measurement error, the bias would be toward the null, suggesting that the effect of doxycycline seen in this study is, if anything, underestimated. Moreover, in a situation where the specificity of measurement of the outcome is 100%, decreased sensitivity of the outcome measurement, as long as nondifferential with respect to exposure, will not affect the measure of association [29]. In this case, it is likely that the specificity of CDI diagnosis was high as stool samples generally are ordered only in patients with symptoms consistent with *C. difficile*.

In this study, receipt of additional antibiotics did not appear to confer increased risk of CDI. This may be in part due to the fact that receipt of ceftriaxone was a requirement for membership in the cohort, and thus, all individuals in the cohort had an increased risk of CDI at baseline. For the same reason, it may have been difficult to estimate the increased risk of CDI specifically due to duration of ceftriaxone. We found that white race and female gender confer increased risk of CDI. The explanation for this is unclear at this time, though recent data suggests that peripartum women are a previously unrecognized risk group [30]. Because San Francisco General Hospital is the major trauma center for San Francisco County, one possibility is that trauma patients, who are more commonly male and nonwhite, are at lower risk for CDI than nontrauma patients [31, 32]. Though we attempted to control for this by adjusting for surgical admissions, not all surgical admissions were due to trauma, so the association between gender and race may have been confounded by the mix of trauma patients. We also found hospitalization to be a strong risk factor for CDI development. While exposure to the hospital is known to increase risk of CDI, the high hazard observed in this study may also be due to the fact that hospitalized patients who develop diarrhea are more likely to be tested for CDI than those who have been discharged [33]. This increased likelihood of testing could result in a form of measurement bias, which is why our multivariate model included inpatient status.

There were several limitations of this study in addition to the ascertainment of the outcome. The antibiotic data were limited to those administered to inpatients. Antibiotics received before or after hospitalization were not recorded. This may have led to an underestimation of the risk of additional antibiotics and residual confounding due to misclassified antibiotic exposure. Because ceftriaxone plus azithromycin is the preferred therapy for patients with CAP being admitted to the intensive care unit, the specific analysis of risk of CDI with doxycycline plus ceftriaxone versus a macrolide plus ceftriaxone may have been biased due to incomplete control for severity of illness. However, the results of this analysis were consistent with the more general analysis of the protective effect of doxycycline.

A further limitation was that information about strain of *C. difficile* was unavailable during the time of this study, as our institution does not routinely test for strain. There were no clear outbreaks during the period under study.

Notwithstanding these limitations, the main finding of our study that doxycycline is associated with lower risk of CDI in hospitalized patients receiving ceftriaxone is robust, biologically plausible, and largely consistent with data from other studies. These results encourage a revisitation of the recommended treatment algorithm for patients with CAP as utilization of doxycycline, as a first-line antibiotic may lead to decreased burden of CDI in these patients [26].

Notes

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