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MAJOR ARTICLE

Influence of Antibiotic Exposure Intensity on the Risk of *Clostridioides difficile* Infection

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Background Antibiotics are a strong risk factor for *Clostridioides difficile* infection (CDI), and CDI incidence is often measured as an important outcome metric for antimicrobial stewardship interventions aiming to reduce antibiotic use. However, risk of CDI from antibiotics varies by agent and dependent on the intensity (i.e., spectrum and duration) of antibiotic therapy. Thus, the impact of stewardship interventions on CDI incidence is variable, and understanding this risk requires a more granular measure of intensity of therapy than traditionally used measures like days of therapy (DOT).

Methods We performed a retrospective cohort study to measure the independent association between intensity of antibiotic therapy, as measured by the antibiotic spectrum index (ASI), and hospital-associated CDI (HA-CDI) at a large academic medical center between January 2018 and

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March 2020. We constructed a marginal Poisson regression model to generate adjusted relative risks for a unit increase in ASI per antibiotic day.

Results We included 35,457 inpatient encounters in our cohort. Sixty-eight percent of patients received at least one antibiotic. We identified 128 HA-CDI cases, which corresponds to an incidence rate of 4.1 cases per 10,000 patient-days. After adjusting for known confounders, each additional unit increase in ASI per antibiotic day is associated with 1.09 times the risk of HA-CDI (Relative Risk = 1.09, 95% Confidence Interval: 1.06 to 1.13).

Conclusions ASI was strongly associated with HA-CDI and could be a useful tool in evaluating the impact of antibiotic stewardship on HA-CDI rates, providing more granular information than the more commonly used days of therapy.

Keywords: *C. difficile*, antimicrobial stewardship, antibiotic spectrum index, healthcare-associated infections

INTRODUCTION

Clostridioides difficile infection (CDI) causes nearly half a million diarrheal illnesses annually in the United States (1), and severe sequalae can include bowel perforation, toxic megacolon, bloodstream infections, and nearly a twofold increase in the risk of death for all hospitalized patients with CDI compared to those without (2, 3). Despite effective treatment, one in five individuals will have a recurrence in 2-8 weeks (4). Hospital-associated *C. difficile* infection (HA-CDI) is a major source of global morbidity, with an estimated 2.24 cases per 1000 hospital admissions each year (5). CDI prevention requires a multi-faceted approach, but efforts to reduce broad-spectrum antibiotic exposures through antimicrobial stewardship play an important role (6-10).

CDI incidence is an important outcome often evaluated following antimicrobial stewardship program (ASP) interventions due to the high risk of CDI attributed to broad spectrum antibiotic therapy and the focus of ASPs on reducing excess broad-spectrum antibiotic use. Because the risk of CDI conferred by antibiotics varies by agent, with fluoroquinolones, clindamycin, and later-generation cephalosporins associated with higher levels of risk (11), traditionally used measures of antibiotic use, such as days of therapy (DOT), fail to capture complete information about the intensity of antibiotic therapy (i.e. the overall spectrum of activity for antibiotics or combinations of antibiotics over time). As an alternate tool to evaluate antibiotic stewardship, Gerber at al. developed the antibiotic spectrum index (ASI) to as a measure of antibiotic exposure weighted by spectrum of activity (12). ASI was developed by surveying a panel of experts on the coverage that individual antibiotics provide against a specified list of clinically important pathogens in the hospital setting. While ASI has previously been applied to other clinical outcomes (13), it has not been applied specifically to CDI.

To better support ASP intervention evaluations, we performed a retrospective cohort study to measure the independent association between intensity of antibiotic therapy, as measured by the ASI, and hospital-associated CDI (HA-CDI). We hypothesized that HA-CDI would be strongly associated with increasing ASI, and that ASI would more accurately predict HA-CDI risk compared to the more commonly used days of therapy (DOT).

METHODS

Study Design and Data Source

We established a retrospective cohort of inpatients admitted to Oregon Health & Science University (OHSU) Hospital between February 25, 2018 and March 23, 2020. OHSU Hospital is a 576-bed academic medical center in Portland, Oregon. We established our study cohort as adult inpatients at risk for HA-CDI. The study cohort was limited to persons 18 years and older and excluded those with known recurrent or community-onset CDI, and those with hospital stays of less than four calendar days, as these individuals are not eligible to be diagnosed with HA-CDI (Figure 1). Excluded patients were still eligible to contribute to *C. difficile* colonization pressure (defined below). To detect instances of recurrent CDI, we reviewed data from 8-weeks prior to the index admission at OHSU. We collected data on demographics, diagnoses, and medications from the Pharmacy Research Repository, a longitudinal repository of patient healthcare data developed in partnership with the OHSU Research Data Warehouse and supported by the Oregon Clinical and Translational Science Institute. These data have been validated and used in previous epidemiologic studies of medication utilization and treatment outcomes (14).

Hospital-associated cdi

Our primary outcome was incident, non-recurrent HA-CDI, which we identified using a combination of medication administration and laboratory testing data (Box 1). Consistent with US Centers for Disease Control and Prevention HA-CDI definitions, we considered incident CDI to be hospital-associated if the date of first anti-*C. difficile* antibiotic administration or stool specimen sample collection from the positive *C. difficile* laboratory test (stool toxin assay or molecular PCR) fell on hospital day 4 or later. We considered CDI non-recurrent if no prior CDI events were identified at the index facility in the 8 weeks before the index CDI diagnosis date. We also performed a validation study of our case definition through comprehensive chart review and determined that our algorithm detected HA-CDI with 94% sensitivity (95% confidence interval: 87-98), 100% specificity (96-100), and 97% overall accuracy (93-99) (15).

Antibiotic Spectrum Index and Days of Therapy

Our primary exposure variable was antibiotic spectrum index (ASI) per antibiotic day, which was developed by Gerber et al. and represents the intensity of antibiotic therapy in our study (12). For antibiotic agents that were not evaluated in the original development of the ASI, we applied the

same criteria to assign a spectrum index after consulting the literature and infectious disease pharmacists and physician coauthors (KJT, HP, and LCS). We aggregated a patient's ASI by summing ASI scores for each individual agent across all days of therapy or until the specimen collection date associated with an HA-CDI diagnosis. Finally, we divided the total ASI for a single hospital encounter by the patient's total number of antibiotic days to create our primary exposure variable. We also calculated DOT, which was defined as receipt of a singular systemic antibiotic agent on a calendar day, independent of the number of doses or the amount of antibiotic given (11, 16). We summed all DOT for each patient's encounter. A single *antibiotic day* was any calendar day that a patient received at least one DOT.

Time at-risk and Colonization Pressure

A patient in our cohort was considered at risk for HA-CDI for the entire hospitalization or until a CDI diagnosis. We defined colonization pressure as the total daily number of individuals with CDI or a *C. difficile* positive laboratory test present on the ward during each patient's time at risk. Any patient in our overall patient population (including those excluded from our study cohort) was eligible to contribute to colonization pressure for the 14 days after initiation of first CDI treatment/positive test or until hospital discharge. We summed the daily number of CDI and/or *C. difficile* test-positive patients by hospital ward for every day a patient was present on the ward, which we defined as *case-days* of colonization pressure, an independent risk factor for HA-CDI (17, 18). We then divided case-days by days at risk to calculate average colonization pressure per patient-day at risk.

Additional covariates/potential confounders

We evaluated several other potential confounders for inclusion in our final model. These include, during the current/index encounter, demographic factors (age, sex, race, ethnicity), pharmacological risk factors (proton pump inhibitors, H2-receptor antagonists, corticosteroids, non-steroidal anti-inflammatory drugs), and clinical risk factors (nasogastric tube placement, gastrointestinal procedures, chemotherapy, previous hospitalizations). We also calculated the Elixhauser comorbidity index, which categorizes patient comorbidities based on ICD-10-CM codes.

Statistical analysis

We performed univariable analysis on each study variable to explore distributions and identify any missing data or potential outliers. We then examined bivariable associations between our primary exposure, outcome, and covariates to confirm variable relationships in our conceptual model (Appendix Figure 1). For bivariable comparisons, we used the Pearson chi-square test to test for differences between categorical variables and the two-sample t-test or Kruskal-Wallis test for differences between continuous variables.

We utilized a multivariable Poisson regression model to evaluate the independent association between antibiotic intensity (ASI per antibiotic day) and risk of CDI. We modeled our CDI outcome as binary, and the primary predictor (ASI per antibiotic day) as continuous. To account for clustering due to multiple visits by the same patient, we used a generalized estimated equations approach (GEE), building a marginal model with robust covariance estimation to generate relative risks. To describe average differences in risk, we calculated adjusted predictive margins by varying ASI per antibiotic day values corresponding to common antibiotic regimens as well as the average marginal effect of ASI per antibiotic day on HA-CDI. We also calculated number needed to harm values and 95% confidence intervals to provide clinical applicability to our findings. To ensure adequate control for confounding, we utilized the "disjunctive cause criterion" proposed by VanderWeele, which recommends controlling for all covariates that cause the exposure or outcome regardless of statistical significance (19). Based on empirical evidence, the following confounders were included in our full regression model *a priori*: time at-risk , age (4, 20), sum of Elixhauser comorbidities (20-22), days hospitalized in the previous 8 weeks (23, 24), inpatient antibiotic use in the previous 8 weeks , proton pump inhibitor or H2-receptor antagonist use (20, 22, 25), nasogastric tube placement (9, 20), other gastrointestinal procedures (9), corticosteroid use (22), chemotherapy (4, 26), source of hospital admission (Emergency Department, other healthcare facility, non-healthcare) (27), and *C. difficile* colonization pressure (17, 28). All data management and statistical analyses were performed using SAS v.9.4.

RESULTS

There were 75,056 inpatient encounters over the 2-year study period. After applying our exclusion criteria, 35,429 (47%) inpatient encounters remained to form our study cohort. Of our overall population cohort, 20% were under 18 years old, 44% had hospitalizations of less than 4 days, and 425 (0.5%) had either community-acquired or known recurrent CDI and were thus excluded (see Figure 1).

The cumulative incidence of HA-CDI in the study cohort was 0.36% or 4.1 cases per 10,000 patient-days. The median number of hospital days to HA-CDI diagnosis was 10 (interquartile range [IQR] = 7-16) days. Sixty-eight percent of our study population received at least one antibiotic during their hospitalization, with a median of 2 days of therapy (IQR = 0-7) and approximately 4.4 ASI units per antibiotic day (Table 1). Cephalosporins were the most commonly administered antibiotic class (59%) followed by penicillins (19%), macrolides (7%), and fluroquinolones (4%). The most common antibiotic agents administered were cefazolin (35%), ceftriaxone (9.5%), and cefepime (7.8%). Detailed antibiotic use is summarized in Appendix Table 1 and Appendix Table 2. Study patients were at risk for HA-CDI for a median of 6 days (IQR = 5-9) and had a median of 2 comorbidities (IQR = 1-3). Fifty-seven percent of our study sample received a proton pump inhibitor or H2 receptor antagonist during their hospitalization and 9%

had a nasogastric tube placed. Study patients experienced a median of 1 case-day of *C. difficile* colonization pressure (IQR = 0-5) (Table 1).

There were no significant differences between patients with HA-CDI and patients without CDI by sex, age, race, or ethnicity (Table 1). Of the 128 patients with HA-CDI, 119 (93%) received at least one antibiotic during the encounter (excluding CDI treatment drugs), compared to 68% of patients without CDI. Antibiotic therapy for patients with HA-CDI showed both longer median durations of therapy (8 vs 2 DOT) and broader spectrum/more intense therapy (mean ASI per antibiotic day 6.9 vs 4.4) compared to those without CDI. The HA-CDI group experienced 10-fold greater colonization pressure, both by total case-days (10 vs 1) and case-days per hospital day (1.0 vs 0.1) compared to those without CDI.

According to our fully adjusted model, each additional unit increase in ASI per antibiotic day was associated with 1.09 times the risk of HA-CDI (Relative Risk [RR] = 1.09, 95% Confidence Interval [CI]: 1.06-1.13) (Table 2). A 5-unit increase, which is the equivalent of receiving vancomycin or ceftriaxone per antibiotic day, was associated with a 1.55 times increased risk of HA-CDI compared to no antibiotic (RR = 1.55, 95% CI: 1.31-1.84). Relative risks for the other key risk factors in our model are summarized in Table 2.

The estimated baseline HA-CDI risk was 0.2% (95% CI: 0.14-0.26) according to our fully-adjusted model. Each additional ASI point per antibiotic day is associated with a 0.03% change in absolute risk on average (risk difference = 0.03%, 0.02-0.04). We provide examples of the CDI risk conferred by frequently used antibiotics, adjusted risk differences, number needed to harm (NNH) values, and adjusted relative risks in Appendix Table 3. From our set of example antibiotic courses, NNH values ranged from 899 (95% CI: 690-1287) for the difference between vancomycin (or any ASI=5 antibiotic) and no antibiotics, and 232 (160-422), for the difference between a vancomycin/piperacillin-tazobactam combination (13 ASI) and no antibiotics. The NNH for piperacillin-tazobactam, a well-known, high-risk agent for CDI that was administered to more than 2,700 patients during our study period, was estimated as 425 (325-611). This means that eliminating 425 courses of piperacillin-tazobactam from our average patient population would theoretically prevent one occurrence of HA-CDI. We also provide examples of NNH values for antibiotic de-escalation and mono vs combination therapy (Appendix Table 4). Compared to a 7-day course of piperacillin-tazobactam, de-escalating 1057 patients on hospital day 3 from piperacillin-tazobactam to ceftriaxone would prevent one HA-CDI case (NNH = 1057, 747-1808), as would de-escalating 578 patients from meropenem to ceftazidime on day 3 (NNH = 578, 398-1053). Treating 633 patients with azithromycin instead of a ceftriaxone-azithromycin combinations for 5 days would also theoretically prevent one HA-CDI occurrence (NNH = 633, 445-1086).

DISCUSSION

ASI was strongly associated with HA-CDI. After adjusting for known confounders, each additional unit of ASI per antibiotic day was associated with approximately a 10 percent increase in HA-CDI risk on a relative scale, and 0.03% change on an absolute scale. Our results illustrate the utility of ASI in quantifying the risk of HA-CDI at the population level. Attributable risk and number needed to harm values also provide tools for estimating CDI reduction following stewardship interventions.

While observed absolute changes in risk were small, and thus, NNH values large, reduction in HA-CDI is still meaningful given the high frequency of antibiotic therapy among hospitalized patients and associated morbidity and mortality caused by CDI. For example, more than 2,700 courses of piperacillin-tazobactam (NNH = 486) were administered during our study period. Additionally, due to the importance of colonization pressure, prevention of a single CDI case is important in the healthcare environment as *C. difficile* is transmitted via person-to-person or environmental contact (4). We found that each additional case-day of colonization pressure doubles the risk of HA-CDI, controlling for other known risk factors. This is consistent with the literature stating that colonization pressure significantly impacts CDI epidemiology, independently from inpatient antibiotic use (17, 18, 29). Finally, a single additional HA-CDI case could also have a significant impact on the CDC Standardized Infection Ratio (SIR), especially in low HA-CDI incidence environments (e.g. only a few HA-CDI cases per month), which could have implications in HA-CDI tracking and planning of interventions (30).

We also established that ASI provides information beyond DOT. If we utilize the same fully adjusted model and substitute 1) number of antibiotic days or 2) days of therapy for ASI per antibiotic day as our primary predictor, the antibiotic days or DOT variable becomes completely insignificant in the model, which suggests that inclusion of ASI is important and provides information beyond DOT in our fully adjusted model. Furthermore, our ASI per antibiotic day variable fit our model better than DOT alone according to quasi-likelihood information criterion (QIC) values (996 vs 1078) (31).

The goal of this research was to inform antibiotic stewardship activities. Stewardship involves active monitoring and evaluation of antibiotic use as well as enacting interventions designed to achieve an overall reduction in antibiotic use and/or reduction in the use of broad-spectrum antibiotics in favor of narrower-spectrum agents (32, 33). While early evaluations of ASP interventions focused on process measures and cost, a shift in focus towards clinical and patient-centered outcomes when evaluating ASP interventions has rendered CDI an important clinical outcome due to its strong association with antibiotic therapy in hospital settings (34). However, evidence has been mixed as to the impact of ASP interventions on CDI incidence. In a meta-analysis by Baur and colleagues, 5 of 11 studies did not report a significant association between ASP interventions and reductions in CDI despite reductions in overall antibiotic use (7). Another meta-analysis by Mijovic and colleagues reported a significant decrease in CDI incidence in 15 of

24 studies. The authors suggest that reliance on quasi-experimental studies constitutes the main limitation in evaluating the ASP-CDI association (35). Because CDI risk is multifactorial, with antibiotic therapy, person-to-person-transmission, environmental sources, community acquisition, and medical comorbidity components all contributing to risk, it is difficult to measure the impact of ASP interventions on CDI rates (36). The context in which these interventions are deployed likely has major impact on the CDI rate; therefore, it is critical that we better understand the causal pathways, attributable risks, and interplay between key risk factors so we can accurately evaluate the likelihood of intervention success. We believe that our study provides valuable addition to the scientific literature in understanding these complexities.

The CDI burden at our institution is relatively low compared to the national burden. In a 2020 meta-analysis, Mara et al. reported an average of 8.3 HA-CDI cases per 10,000 patient days in the US (37), which is considerably higher than the 4.4 cases per 10,000 patient-days observed at our institution during the study period. Further application of ASI to data from other institutions is necessary to determine the generalizability of our results. However, using ASI allows us to granularly describe the risk of HA-CDI from antibiotics without requiring a large, multifacility dataset. An additional limitation is ASI was not developed specifically for CDI and antibiotics with the same ASI (e.g., clindamycin and sulfamethoxazole-trimethoprim, both with an ASI of 4), could confer very different CDI-specific risks, thus further refinement of the ASI could improve its ability to capture antibiotic-attributable risks for HA-CDI.

We observed that the risk of HA-CDI increases with intensity of antibiotic exposure, as defined by ASI per antibiotic day. Utilizing ASI, and aiming for overall reductions at the facility level, could provide a clear and achievable goal for antibiotic stewardship activities. Additional research is also needed to explore if ASI could also be utilized as a tool for individual-level decision making around prescribing choices. Most existing literature highlights the clinical benefits of empiric prescribing. Our study is among the first to estimate number needed to harm values for commonly used antibiotics and combinations of antibiotics, and provides more complete information on potential adverse implications of antibiotic prescribing. Our study demonstrates that ASI is an excellent predictor of HA-CDI and that ASI provides information beyond days of antibiotic therapy. The antibiotic spectrum index is a valuable tool that can be utilized for evaluation of antibiotic stewardship as well as CDI reduction efforts.

Author contributions

The study was conceived of and designed by MJR and JCM. CMM provided initial data abstraction and support. MJR undertook all data analysis. JPF, ETL, and JCM provided overall analytical support. LCS, KJT, and HP provided clinical expertise, and JSG initially conceived the antibiotic spectrum index. All authors contributed substantially to manuscript revisions. MJR had full access to all study data and takes responsibility for data integrity and accuracy of the data analysis.

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Conflicts of interest: None of the authors have any conflicts of interest to disclose

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Box 1. Definition for incident hospital-associated CDI cases

Anti-CDI antibiotic therapy initiated on hospital day four or later	Oral/rectal Vancomycin Metronidazole Fidaxomicin
AND	
Positive laboratory test; sample collected on hospital day four or later	PCR, Stool toxin A, Toxin B
Incident Case Definition	
Non-recurrent – no known CDI in the previous 8 weeks	

Table 1. Patient and encounter characteristics in the study cohort by HA-CDI status – January 1, 2018 through March 23, 2020 (N=35,457)

	HA-CDI (n=128)	No CDI (n=35329)	*P* value
Sex, n (%)			
Male	66 (51)	16743 (47)	0.35
Female	62 (49)	18586 (53)	
Age, mean (SD)	58.4 (17.0)	56.4 (19.0)	0.24
median (IQR)	62 (48.5-70)	59 (41-71)	0.26
Race, n (%)			
White	112 (88)	30731 (87)	0.73
Black	4 (3.0)	932 (2.6)	
Asian	5 (3.7)	1012 (2.9)	
Other/unknown/ multiple	7 (5.2)	2654 (7.5)	
Ethnicity, n (%)			
Hispanic or Latino	4 (3)	2530 (7)	0.13
Not Hispanic or Latino	118 (93)	30481 (86)	
Unknown	6 (4)	2318 (7)	
Time at-risk, median IQR	11 (7-16.5)	6 (5-9)	<0.0001
Sum of Elixhauser comorbidities	3 (1.5-4)	2 (1-3)	<0.0001
Antibiotics			
Any antibiotic	119 (93)	24107 (68)	<0.0001
No. Antibiotics median, IQR	2 (1-3)	1 (0-2)	<0.0001
Median DOT (IQR)	8 (2-14)	2 (0-7)	<0.0001
Total ASI median (IQR)	42.5 (13.5-80)	8 (0-36)	<0.0001
ASI per DOT mean (SD)	5.4 (2.2)	3.2 (2.6)	<0.0001
ASI per day at risk mean (SD)	4.1 (3.0)	2.9 (3.6)	<0.0001
ASI per antibiotic day mean (SD)	6.9 (3.5)	4.4 (4.1)	<0.0001
Colonization pressure			
Total case-days median (IQR)	10 (4-33)	1 (0-4)	<0.0001
Case-days per day at-risk	1.0 (0.3-1.8)	0.1 (0-0.6)	<0.0001
Other drugs, n (%)			
PPI or H2RA	109 (85)	19990 (57)	<0.0001
Corticosteroids	50 (39)	8807 (25)	0.0001
Chemotherapy agents	52 (40)	9372 (27)	0.0003
Procedures, n (%)			
Nasogastric tube placement	30 (23)	3099 (8.8)	<0.0001
Other gastrointestinal procedures	22 (17)	1445 (4)	<0.0001
Chemotherapy procedures	27 (21)	1917 (5.4)	<0.0001
Admission source, n (%)			
Non-healthcare or not listed	17 (13)	7036 (20)	0.03
Emergency department	25(20)	8582 (24)	

Healthcare facility	86 (67)	196711 (56)	
Pre-admission risk factors^			
No. prior inpatient encounters, n (%)			
Zero	117 (91)	30746 (87)	0.10
One	11 (9)	3470 (10)	
Two or more	0 (0)	1113 (3)	
Prior Hospital days, n (%)			
Zero	117 (91)	30746 (87)	0.26
1 to 7	6 (4)	1875 (5)	
8+	5 (4)	2708 (8)	
Prior Antibiotic days of therapy, n (%)			
Zero	118 (92)	32099 (91)	0.87
1 to 7	5 (4)	1580 (4)	
8+	5 (4)	1650 (5)	

Abbreviations: IQR, interquartile range; SD, standard deviation; DOT, days of therapy; ASI, antibiotic spectrum index; PPI, proton pump inhibitor; H2RA, H2 receptor antagonist; GI, gastrointestinal; ED, emergency department
^Pre-admission risk factors for the previous 8 weeks at OHSU, excluding the current hospitalization

Table 2. Adjusted relative risks for significant CDI risk factors identified in our final model

	Relative Risk (95% CI)
ASI per antibiotic day[a]	1.09 (1.06 – 1.13)
Time at-risk[b]	1.007 (0.998– 1.016)
Number of comorbidities[c]	1.35 (1.22 – 1.50)
PPI/H2RA	2.53 (1.46 – 4.39)
NG tube placement	1.76 (1.06 – 2.93)
GI procedures	2.28 (1.37 – 3.81)
Chemotherapy	2.02 (1.27 – 3.22)
Colonization pressure[d]	2.09 (1.92 – 2.27)

Full model adjusted for the above variables and the following variables that were not significant ($p > 0.05$) in our model: age, number of days hospitalized in the previous 8 weeks, inpatient antibiotic use in the previous 8 weeks, corticosteroid use, and source of hospital admission (Emergency Department, other healthcare facility, non-healthcare); abbreviation: ASI – antibiotic spectrum index, PPI/H2RA – proton pump inhibitor or H2 receptor antagonist

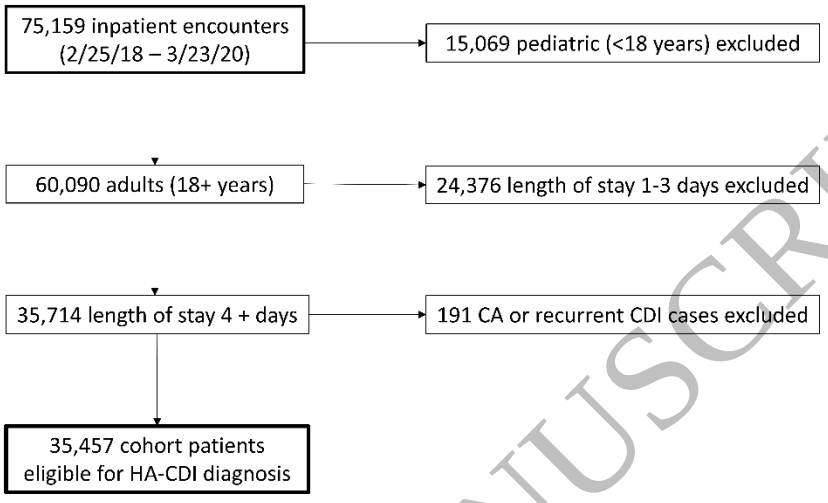
[a]per unit of ASI per antibiotic day

[b]per day at-risk

[c]per each additional Elixhauser comorbid condition

[d]per case-day of colonization pressure per hospital day

Figure 1. Construction of our study cohort (February 25, 2018 – March 23, 2020)



Note: Excluded patients still eligible to contribute to *C. difficile* colonization pressure