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Evaluating Clostridioides Difficile Infection (cdi) Risk Factors By Comparing The Use Of Piperacillin/tazobactam, Cefepime, And Ceftazidime

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Abstract

Introduction: Over the past several years, *Clostridioides difficile* infection (CDI) incidence has been rising. The primary risk factor for CDI is antibiotic use. Many studies indicate that penicillin drugs are among the low-risk antibiotic classes associated with CDI whereas cephalosporin drugs are among the high-risk antibiotic classes. However, there is variation in studies evaluating the healthcare-associated CDI (HA-CDI) risk associated with antibiotics within a class and limited data comparing the use of penicillin versus cephalosporin drugs.

Methods: An observational cohort study was performed using patient data from BH and YNHH. Minitab (Version 18) was used to perform survival analysis and multivariate logistic regression. Charlson comorbidity index scores were utilized to control and adjust for underlying comorbidities, and adjusted odds ratios were calculated using backwards elimination.

Results: Data collected from a 5-year period between February 1, 2013 and June 1, 2018 revealed that piperacillin/tazobactam exposure at YNHH was associated with a higher CDI risk than penicillin exposure ($p = 0.016$). Additional covariates included H2A use (OR = 0.497, $p = 0.027$), Charlson comorbidity index scores (OR = 0.848, $p = 0.025$), and longer duration of hospital admission (OR = 1.038, $p < 0.001$).

Discussion: The findings in the YNHH cohort may justify an investigation into de-escalation of piperacillin/tazobactam empiric therapy intended for suspected infection caused by Gram-negative bacteria. Further study is needed to better address the association between the covariates and CDI risk in the BH cohort. Next steps may include an aggregate analysis of CDI risk between penicillin drugs and cephalosporin drugs along with a closer exploration of the facility and individual-level factors at both hospitals.

Acknowledgements

First and foremost, I would like to sincerely thank my advisors for this project, Dr. Richard A. Martinello, Dr. Jeffrey E. Topal, and Dayna McManus. This project would not have been possible without their continuous guidance and feedback. I would like to thank my thesis reader, Dr. Louise-Marie Dembry, for her incredibly valuable feedback throughout this process. I would also like to thank Dr. David R. Peaper for his help with obtaining the *C. difficile* assay results and Jose Rivera-Vinas for his help with performing the data analysis. Lastly, I want to thank the Yale Joint Data Analytics Team (JDAT) for providing the electronic health record data extract for the duration of the 5-year study period.

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Table 1: BH Demographics

	BH Piperacillin/tazobactam (N = 946)	BH Cefepime (N = 2720)	P-value
Patient Demographics			
Age, mean (SD)	64.8 (19.0)	69.4 (17.7)	< 0.001
Male, n (%)	510 (53.9)	1354 (49.8)	0.029
Charlson Comorbidity Index Score, mean (SD)	2.4 (2.4)	2.8 (2.4)	< 0.001
Days of Hospital Admission, mean (SD)	14.0 (11.2)	10.8 (9.1)	< 0.001
Patient Characteristics			
Days of Therapy, mean (SD)	4.5 (2.0)	4.9 (2.3)	< 0.001
High-Risk Antibiotic Therapy, n (%)	613 (64.8)	1674 (61.5)	NS
Proton-Pump Inhibitor Therapy, n (%)	442 (46.7)	1583 (58.2)	< 0.001
Histamine-2-Receptor Antagonist Therapy, n (%)	469 (49.6)	1947 (71.6)	< 0.001
C. difficile **Assay**			
Tested, n (%)	122 (12.9)	157 (5.8)	< 0.001
Positive, n (%)	12 (1.3)	25 (0.9)	NS
Negative, n (%)	110 (11.6)	132 (4.9)	< 0.001
Null, n (%)	824 (87.1)	2563 (94.2)	< 0.001

Table 1: Demographics for BH piperacillin/tazobactam and BH cefepime cohorts.

Table 2: BH Piperacillin/Tazobactam Multivariate Regression Model

Source	Odds Ratio[1]	95% CI[1]	P-value[1]	Odds Ratio[2]	95% CI[2]	P-value[2]
High-Risk Antibiotic Therapy	6.636	(0.815, 49.652)	0.024	6.066	(0.780, 47.190)	0.024
PPI Therapy	0.542	(0.161, 1.824)	0.31	-	-	-
H2A Therapy	1.548	(0.485, 4.943)	0.457	-	-	-
Male	0.565	(0.177, 1.804)	0.331	-	-	-
Charlson Comorbidity Index Score	1.224	(1.023, 1.463)	0.043	1.247	(1.048, 1.484)	0.024
Age	1.003	(0.969, 1.038)	0.853	-	-	-
Days of Hospital Admission	1.028	(0.993, 1.065)	0.161	-	-	-

Table 2: The multivariate logistic regression model for the BH piperacillin/tazobactam group. Statistical significance is determined by a p-value of < 0.05. The superscript (1) indicates an unadjusted model, whereas the superscript (2) indicates the adjusted model through backwards elimination.

Table 3: BH Cefepime Multivariate Regression Model

Source	Odds Ratio[1]	95% CI[1]	P-value[1]	Odds Ratio[2]	95% CI[2]	P-value[2]
High-Risk Antibiotic Therapy	2.029	(0.807, 5.105)	0.113	-	-	-
PPI Therapy	1.47	(0.631, 3.426)	0.362	-	-	-
H2A Therapy	0.426	(0.193, 0.940)	0.038	0.426	(0.194, 0.938)	0.038
Male	0.805	(0.363, 1.782)	0.591	-	-	-
Charlson Comorbidity Index Score	1.074	(0.919, 1.256)	0.376	-	-	-
Age	1.018	(0.991, 1.044)	0.178	-	-	-
Days of Hospital Admission	1.040	(1.012, 1.069)	0.015	1.040	(1.013, 1.068)	0.012

Table 3: The multivariate logistic regression model for the BH cefepime group. Statistical significance is determined by a p-value of < 0.05. The superscript (1) indicates an unadjusted model, whereas the superscript (2) indicates the adjusted model through backwards elimination.

Table 4: YNHH Demographics

	YNHH Piperacillin/tazobactam (N = 5239)	YNHH Ceftazidime (N = 3004)	P-value
Patient Demographics			
Age, mean (SD)	63.5 (17.6)	64.3 (17.2)	NS
Male, n (%)	3074 (58.7)	1600 (53.3)	< 0.001
Charlson Comorbidity Index Score, mean (SD)	2.8 (2.4)	2.7 (2.3)	NS
Days of Hospital Admission, mean (%)	14.5 (13.4)	14.9 (13.7)	NS
Patient Characteristics			
Days of Therapy, mean (SD)	4.2 (2.0)	4.5 (2.2)	< 0.001
High-Risk Antibiotic Therapy, n (%)	3194 (61.0)	1753 (58.3)	0.020
Proton-Pump Inhibitor Therapy, n (%)	2460 (47.0)	1324 (44.1)	0.011
Histamine-2-Receptor Antagonist Therapy, n (%)	3071 (58.9)	1827 (60.8)	NS
C. difficile **Assay**			
% Tested	683 (13.0)	165 (5.5)	< 0.001
Positive, n (%)	41 (0.8)	12 (0.4)	0.036
Negative, n (%)	642 (12.3)	153 (5.1)	< 0.001
Null, n (%)	4556 (87.0)	2839 (94.5)	< 0.001

Table 4: Demographics for the YNHH piperacillin/tazobactam and YNHH ceftazidime cohorts.

Table 5: YNHH Piperacillin/Tazobactam Multivariate Regression Model

Source	Odds Ratio[1]	95% CI[1]	P-value[1]	Odds Ratio[2]	95% CI[2]	P-value[2]
High-Risk Antibiotic Therapy	1.253	(0.654, 2.402)	0.492	-	-	-
PPI Therapy	0.789	(0.421, 1.476)	0.455	-	-	-
H2A Therapy	0.499	(0.267, 0.931)	0.027	0.497	(0.267, 0.928)	0.027
Male	1.075	(0.572, 2.020)	0.823	-	-	-
Charlson Comorbidity Index Score	0.829	(0.706, 0.973)	0.014	0.848	(0.727, 0.988)	0.025
Age	1.012	(0.994, 1.030)	0.198	-	-	-
Days of Hospital Admission	1.039	(1.026, 1.051)	< 0.001	1.038	(1.025, 1.050)	< 0.001

Table 5: The multivariate logistic regression model for the YNHH piperacillin/tazobactam group. Statistical significance is determined by a p-value of < 0.05. The superscript (1) indicates an unadjusted model, whereas the superscript (2) indicates the adjusted model through backwards elimination.

Table 6: YNHH Ceftazidime Multivariate Regression Model

Source	Odds Ratio[1]	95% CI[1]	P-value[1]	Odds Ratio[2]	95% CI[2]	P-value[2]
High-Risk Antibiotic Therapy	1.555	(0.465, 5.203)	0.464	-	-	-
PPI Therapy	0.246	(0.054, 1.129)	0.039	0.253	(0.055, 1.155)	0.043
H2A Therapy	0.326	(0.098, 1.086)	0.058	-	-	-
Male	0.879	(0.282, 2.739)	0.825	-	-	-
Charlson Comorbidity Index Score	1.156	(0.913, 1.463)	0.245	-	-	-
Age	1.041	(0.997, 1.087)	0.053	1.043	(1.000, 1.088)	0.001
Days of Hospital Admission	1.044	(1.026, 1.063)	< 0.001	1.046	(1.028, 1.065)	0.034

Table 6: The multivariate logistic regression model for the YNHH ceftazidime group. Statistical significance is determined by a p-value of < 0.05. The superscript (1) indicates an unadjusted model, whereas the superscript (2) indicates the adjusted model through backwards elimination.
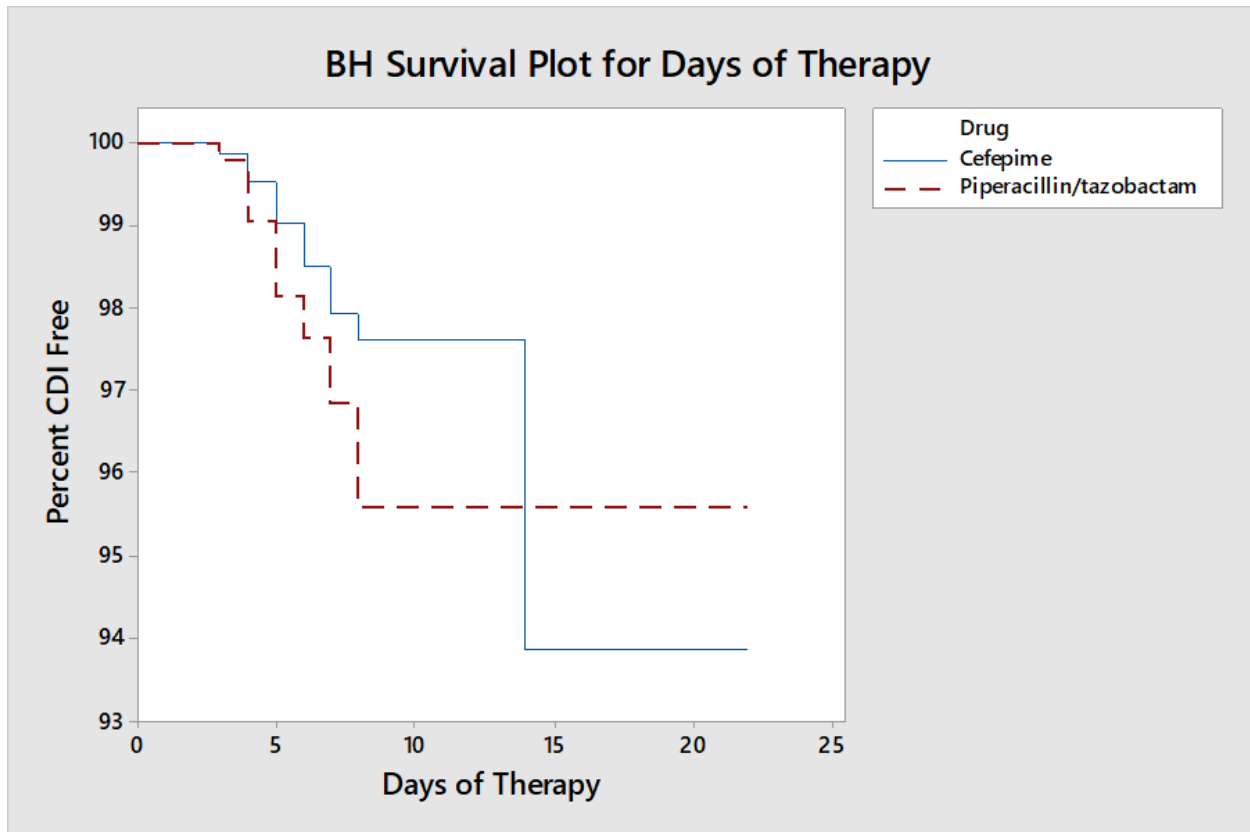
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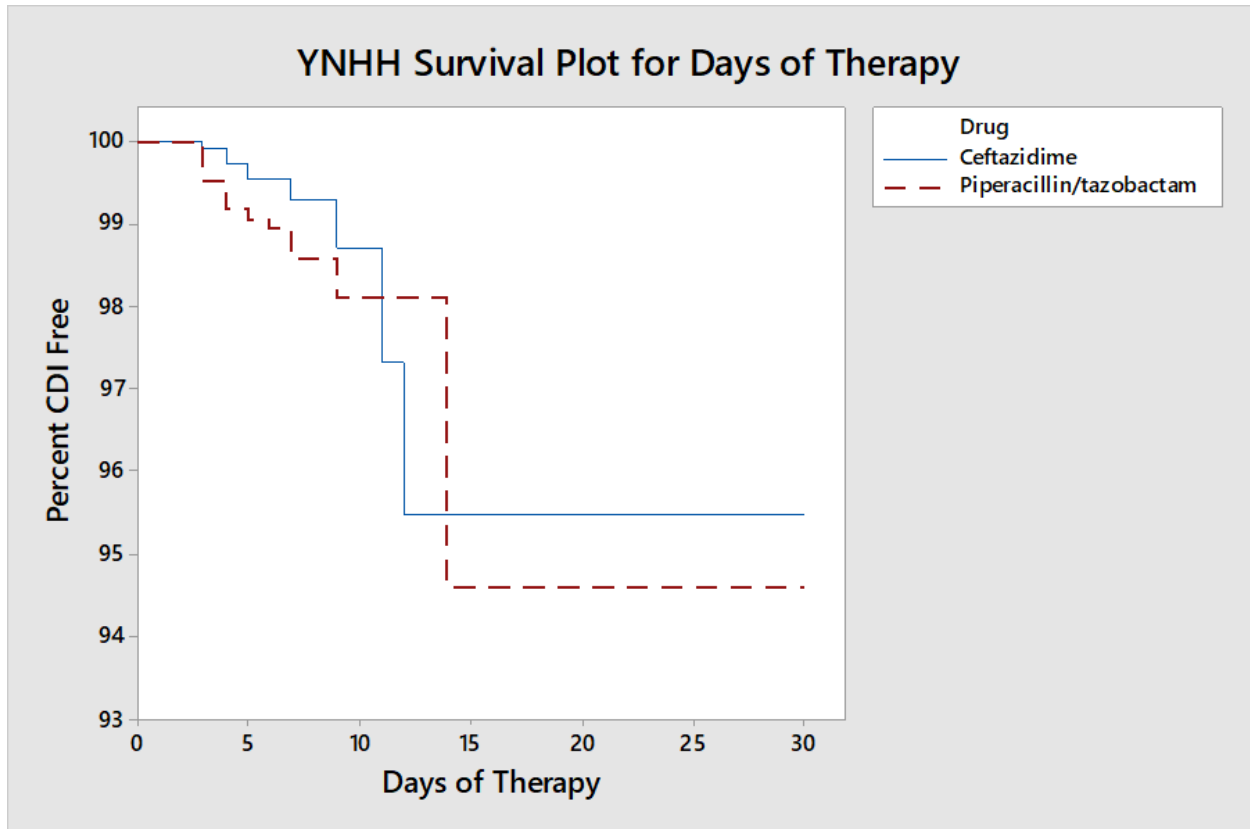
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Introduction

Clostridioides difficile is a gram-positive, anaerobic, and spore-forming bacterium that causes inflammation of the colon, otherwise known as colitis.[1] It is the leading cause of pseudomembranous colitis and antibiotic-associated diarrhea among hospitalized patients.[2] Symptoms characteristic of *Clostridioides difficile* infection (CDI) include abdominal cramping, varying degrees of diarrhea severity, dehydration, weight loss, and fever.[3] Following ingestion, the acid-resistant *C. difficile* spores bypass the stomach's acid barrier and are able to germinate into vegetative cells.[1] The vegetative cells secrete two primary virulent factors: *C. difficile* Toxin A (TcdA) and *C. difficile* Toxin B (TcdB).[1] TcdA, one of the largest bacterial toxins, is a protein enterotoxin that assembles to form pores in cell membranes.[2] TcdB is a cytotoxin that causes a disruption in signal transduction pathways to initiate apoptosis.[2] Together, TcdA and TcdB act to disrupt the intestinal mucosa and are directly responsible for causing characteristic CDI manifestations including pseudomembranous colitis.[2] The primary mode of transmission for CDI is the fecal-oral route in which the bacterial spores may contaminate various surfaces, devices, or additional materials for long durations of time.[4] These spores are mainly transmitted through the hands of healthcare personnel following contact with a contaminated surface.[4]

CDI is divided into three main laboratory classifications: community-onset CDI (CO-CDI), hospital-onset CDI (HO-CDI), and community-onset healthcare facility-associated CDI (CO-HCFA).[5] CO-CDI is defined as the collection of a stool specimen which tested positive for *C. difficile* ≤ 3 days within hospital admission, and HO-CDI is defined as collection of a stool specimen which tested positive for *C. difficile* > 3 days after hospital admission.[5] CO-HCFA is defined as the collection of a stool specimen which tested positive for *C. difficile* ≤ 4 weeks after hospital discharge.[5] Some literature shows that many cases of hospital-associated CDI (HA-CDI)

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are community-onset.[6,7] In cases that are community-onset and healthcare-associated, antibiotic exposure in the hospital setting is likely to trigger infection. As a result, the link between community-associated CDI (CA-CDI) and HA-CDI has become a key focus point in measuring CDI trends in recent years.

Over the past several years, there has been a rise in incidence, prevalence, as well as corresponding morbidity and mortality associated with CDI. [8] In many areas of the United States, *C. difficile* has overtaken methicillin-resistant *Staphylococcus aureus* (MRSA) as the chief pathogen causing healthcare-associated infections (HAIs).[8,9] A 2011 study from the Centers for Disease Control and Prevention (CDC) estimated there to be 493,000 CDI cases a year, out of which 83,000 were recurrent infections and 29,300 cases resulted in death.[8] It has also been reported that out of the 493,000 CDI cases, nearly a quarter (24.2%) were classified as HO-CDI.[10] Between 1996 and 2000, the reported CDI incidence in US acute-care facilities was 30-40 discharges per 100,000 acute-care hospitalizations.[11,12] This incidence doubled in 2003 to 60 discharges per 100,000 acute-care hospitalizations.[11] Additionally, the number of hospital stays with a CDI discharge diagnosis saw a 2.5-fold increase between the years 2000 and 2008.[11] The number of hospital stays with a principal CDI diagnosis[1,13] saw a 3.5-fold increase during the same time period.[11] CDI had comprised approximately 1% of all US hospital admissions in 2009.[11] Moreover, CDI-associated mortality has seen a steady increase over time. A 9-fold increase in the number of deaths with CDI as the primary cause has been observed between 1999 and 2008.[11] Other studies have further stratified the data for CDI-associated mortality by examining trends concerning gastroenteritis-associated deaths. CDI mortality experienced a 5-

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[1] Principal diagnosis – the condition established to be chiefly responsible for the patient's admission to the hospital.

fold increase between 1999 and 2007; *C. difficile* was identified as the main contributor to gastroenteritis-associated deaths in US acute-care facilities.[11]

CDI cases incur excess costs of $4.8 billion in acute care facilities.[14] CDI incurs higher costs by extending the length of hospital admission and increasing the risk for further adverse events such as other HAIs. Some studies show that the average hospital length of admission for secondary CDI diagnoses[2] was more than twice as long than for principal CDI diagnoses.[11,13] Secondary CDI diagnoses incurred a cost more than three times higher than that of principal CDI diagnoses.[11] Three primary hypotheses have been proposed to explain the rising incidence, prevalence, morbidity, and mortality of CDI: inadequate environmental cleaning practices, over and under identification of cases, and permissive indications for initiating antibiotic therapy.[15,16] Many studies pinpoint antibiotic prescribing habits as the primary contributor to the rising CDI rates over time.[17,18,19]

Commensal flora in the human gut play an important role in warding off pathogenic colonization or infection. Secondary bile acids, metabolized by commensal gut bacteria, will in many cases prevent germination of *C. difficile* spores into vegetative cells.[20] The commensal flora typically produce bacteriocins, neutralize toxins, and outcompete pathogens for consuming available nutrients.[20] These native functions are able to prevent vegetative cells from attaching to and colonizing the gut epithelium.[20] These native functions additionally inhibit production of TcdA and TcdB.[20] Antibiotic therapy alters the commensal flora in the gut, thus compromising the integrity of the physical and biochemical barriers in place that prevent CDI.[1,21] Though the specifics of the gut microbiome alterations are not fully understood, several studies propose that

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[2] Secondary diagnosis – concomitant conditions that coexist at the time of admission or that develop during the stay.

there is a decrease in commensal flora, thus weakening the physical and biochemical barriers against CDI.[22,23,24] Due to the change in the commensal flora composition, antibiotic use poses a significant risk for CDI.

CDI risks by antibiotic class vary across studies. In most studies, low risk antibiotics include penicillins, macrolides, and tetracyclines.[25,26] A meta-analysis performed by Brown, et. al. depicted CDI risks stratified by antibiotic class by identifying trends across various studies.[25] HA-CDI studies were excluded as well as studies restricted to only oncology or HIV patients. The meta-analysis aimed to pool together studies showing incident CDI dependent upon antibiotic exposure. CDI risks ranged from an odds ratio of 1.72 to 6.50 for penicillins, an odds ratio of 2.19 to 4.01 for macrolides, and an odds ratio of 0.90 to 1.10 for tetracyclines.[25] Another meta-analysis performed by Deshpande, et. al. followed a similar method.[26] The group focused on community-associated CDI and also sought to identify antibiotic exposure risk factors associated with incident CDI. CDI risks ranged from an odds ratio of 1.89 to 5.57 for penicillins, an odds ratio of 1.91 to 3.39 for macrolides, and an odds ratio of 0.57 to 1.45 for tetracyclines.[26] A common theme across both meta-analyses was the relatively high degree of variation of CDI risk associated with penicillin antibiotics.

Among the penicillin class of antibiotics, studies with piperacillin/tazobactam show inconsistent data regarding its association with CDI risk.[27,28,29] A study conducted by Shah, et. al. examined HA-CDI risk with individual antibiotics within an antibiotic class.[27] Since existing literature depicts a relatively large degree of variation in CDI risk from penicillin exposure, inpatient surgery patients were evaluated for incident CDI. Patients with diarrhea were retrospectively examined for previous antibiotic exposure. The odds ratio for piperacillin/tazobactam ranged from 1.32 to 4.50, once again showing significant variation

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among individual patients.[27] Another cohort study performed by Bow, et. al. looked at oncology and transplant patients with respect to *C. difficile*-associated diarrhea incidence.[29] In a cohort of 265 patients receiving piperacillin/tazobactam therapy, approximately 2.3% developed CDI.[29] Another point of comparison in the study was with an individual antibiotic from a known high-risk antibiotic class.

In most studies, high-risk antibiotics are comprised of cephalosporins, clindamycin, carbapenems, and fluoroquinolones.[25,26,30] The Brown, et. al. meta-analysis showed CDI risks ranging from an odds ratio of 2.20 to 14.90 for cephalosporins and carbapenems, an odds ratio of 6.64 to 31.80 for clindamycin, and an odds ratio of 1.31 to 9.39 for fluoroquinolones.[25] The Deshpande, et. al. meta-analysis showed similar CDI risks ranging from an odds ratio of 1.60 to 12.50 for cephalosporins, an odds ratio of 8.50 to 49.09 for clindamycin, and an odds ratio of 4.38 to 7.28 for fluoroquinolones.[26] While the documented CDI risk associated with clindamycin use has a high degree of variation, the average risk remains high across multiple studies. Although there is a great deal of variation in CDI risk associated with cephalosporin exposure, its odds ratio is much lower when compared to that of other known high-risk antibiotics.

Studies show varying CDI risk associated with ceftazidime and cefepime, third and fourth-generation cephalosporins, respectively.[27,28,29] There are very few studies depicting CDI risk associated with ceftazidime exposure alone, instead grouping ceftazidime in a category of third and fourth-generation cephalosporins. A study conducted by Shah, et. al. documented an odds ratio ranging from 1.72 to 19.1 for cefepime associated CDI risk.[27] The Muldoon, et. al. group has shown an average odds ratio of 2.10 of CDI risk associated with cefepime exposure.[28] The data shows a large degree of variation despite the fact that cephalosporins as a class are typically associated with a high CDI risk. A cohort study carried out by Bow, et. al. shows that

among a cohort of 263 patients receiving cefepime therapy, 6.8% developed CDI.[29] Although some studies show a higher CDI risk with cephalosporins, the variation observed across individual patients brings a significant degree of uncertainty into the equation, especially given the multitude of additional CDI risk factors present in an acute-care setting.

Piperacillin/tazobactam, ceftazidime, and cefepime are β-lactam anti-pseudomonal agents. Piperacillin/tazobactam possesses coverage against Gram-positive, Gram-negative, and anaerobic bacteria.[31,32] Ceftazidime possesses coverage against Gram-negative bacteria; its primary limitation relative to piperacillin/tazobactam is limited Gram-positive and anaerobic coverage.[31,32] Cefepime possesses coverage against both Gram-positive and Gram-negative bacteria, providing some advantages over ceftazidime.[31,32] Cefepime has limited activity against anaerobic bacteria.[31] Depending on the clinical situation, this poses a limitation relative to piperacillin/tazobactam.

In order to evaluate CDI risk factors associated with piperacillin/tazobactam, cefepime, and ceftazidime, the CDI risk associated with their empiric use is evaluated in the two largest hospitals in the Yale New Haven Health System: Bridgeport Hospital (BH) and Yale New Haven Hospital (YNHH). Based on antibiograms and provider preference, cefepime is the preferred broad-spectrum antibiotic for empiric use at BH, and piperacillin/tazobactam is the preferred broad-spectrum antibiotic for empiric use at YNHH. Piperacillin/tazobactam is additionally on the formulary at BH, and ceftazidime is on the formulary at YNHH.

A formulary is defined as a continually updated list of medications and related information, representing the clinical judgment of pharmacists, physicians, and other experts in the diagnosis and/or treatment of disease and promotion of health.[33,34] It makes up one element of a broader formulary system, which includes medication use policies, a pharmacy and

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therapeutics committee, medication use evaluation, and formulary management.[33,34] The formulary system serves the purpose of evaluating medications on an ongoing basis for inclusion and exclusion, establishing guidelines for optimal medication use, developing policies and procedures for prescribing, dispensing, and administering medications.[33] The delivery of changes to the formulary system fall under the jurisdiction of the pharmacy and therapeutics committee.

Formulary access is categorized as either open or closed. An open formulary has no limit or restriction on medications, whereas a closed formulary has a limited list of available medications.[33] When considering the use of several antibiotics, formulary restrictions are often placed to better optimize medication management. Some data suggests that restricting formularies may impose higher healthcare costs by increasing utilization of physician visits and hospitalizations.[33] While the data is the subject of controversy, the impact on healthcare costs is a notable factor in driving changes to the formulary. In order to change a formulary, a member or members of the pharmacy or medical staff must submit a request for formulary addition or deletion.[33] The submission requests are comprised of 1) the agent to be considered for addition or deletion, 2) the rationale for the request, and 3) alternative agents currently on the formulary.[33] There are several patient care and financial considerations that play a role in initiating a formulary change. Patient care considerations primarily include questions regarding medication safety and efficacy, whereas financial considerations mainly include questions regarding the cost of the drug as well as costs associated with stocking the drug that include handling, drug outdates, and shelf space.[33]

In theory, the existing formularies at BH and YNHH should have no significant difference in the risk of acquiring CDI between penicillin (piperacillin/tazobactam) and cephalosporin drugs (cefepime and ceftazidime). Based on current literature, there is

hypothesized to be a significant difference in CDI risk between empiric therapy of the aforementioned penicillin and cephalosporin drugs. The study's primary goal is to evaluate the comparative risk for HA-CDI by comparing the uses of penicillin and cephalosporin drugs. The findings may unveil an increased, significant HA-CDI risk associated with a particular antibiotic that is not reported in existing literature. If an increased HA-CDI risk is observed, it may potentially guide efforts for antibiotic stewardship, advise formulary decisions, and decrease overall patient risk of CDI. Several factors are considered in a formulary shift including a significant difference in CDI risk, any known significant difference in other multidrug-resistant infection risk, and healthcare costs. Additionally, the potential findings may prompt peer hospitals to explore similar studies concerning empiric antibiotic use. As HA-CDI grows in prevalence, clinical research is paramount to optimize antibiotic stewardship. Although extensive literature exists that documents CDI risk associated with antibiotics, few studies include a risk stratification by antibiotic class. Even fewer studies exist that break down members of each antibiotic class to account for variation within an antibiotic class. This study aims to provide more insight into the association between HA-CDI and individual drugs within antibiotic classes to better guide prescribing practices in healthcare settings to prevent HA-CDI and improve patient safety.

Methods

Study Design and Participants

An observational cohort study was conducted at the Yale New Haven Health System (YNHHS) to include patient data at BH and YNHH from February 1, 2013 to June 1, 2018. This timeline sought to encompass documented patient data since the inception of Epic (© 2019 Epic Systems Corporation, Verona, WI) – the electronic medical record utilized at both hospitals. The study reviewed medical records from BH (Bridgeport, CT) a 357-bed academic medical center as well as from YNHH (New Haven, CT), a 1,541-bed tertiary care academic medical center.

Patients who had received ≥ 3 days of piperacillin/tazobactam, cefepime, or ceftazidime therapy were included.[19] Patients in each cohort group were included provided that they were only admitted to the hospital of concern (i.e. patients with separate admissions at BH and YNHH were excluded regardless of time gap). Patients meeting the antibiotic exposure definition were included provided that they only received the antibiotic therapy of concern (i.e. a patient receiving any combination of piperacillin/tazobactam, cefepime, or ceftazidime therapy was excluded). In order to address patients with multiple admissions over a period of time, only the first hospital admission meeting the inclusion criteria was included as a data point along with the rest of the corresponding data points.

Numerous hospital units were excluded: oncology (surgical, medical, hematology), transplant (stem cell, solid organ), and pediatric (oncology, transplant). These exclusions were made since BH does not provide oncology care for patients with acute hematological malignancies or care for stem cell or solid organ transplants. The exclusions were made to standardize the patient populations between both hospitals. As the excluded units care for severely ill and immunocompromised patients, their exclusion from the data set was also to

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ensure the two cohorts are directly comparable. Patients under the age of 18, patients who had been hospitalized for < 2 days, patients who had been hospitalized for ≥ 120 days, and HIV positive patients with a CD4 T-cell count of < 200 were excluded.

The Institutional Review Boards (IRB) of both Bridgeport Hospital and Yale University deemed the study as exempt from IRB approval, designating the study as a quality improvement project.

Definitions

A standard dose of piperacillin/tazobactam is defined as 4.5 g every 6 hours.[31] A standard dose of ceftazidime and cefepime are defined as 2 g every 8-12 hours.[31] Exposure to piperacillin/tazobactam, ceftazidime, or cefepime therapy is defined as ≥ 3 contiguous days of treatment. A positive HA-CDI diagnosis is defined as one made ≥ 48 hours after admission in accordance with the CDC NHSN LabID and each hospital's *C. difficile* assay (see Appendix 1 and 2).[35]

Exposure to high-risk antibiotic therapy is defined as ≥ 3 contiguous days of treatment with a combination or standalone of the following antibiotics on both hospital formularies: ciprofloxacin, moxifloxacin, clindamycin, ertapenem, or meropenem. Other antibiotics administered within the documented high-risk antibiotic classes were not included. Exposure to proton-pump inhibitor (PPI) therapy is defined as ≥ 3 contiguous days of treatment with either of the following agents on both hospital formularies: lansoprazole or pantoprazole. Exposure to histamine-2-receptor antagonist (H2A) therapy is defined as ≥ 3 contiguous days of treatment with famotidine (present on both hospital formularies).

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Data Collection

Patient data from the electronic health record over the course of the five-year study period was extracted by the Yale Joint Data Analytics Team (JDAT), a team handling clinical and research analytics across the Yale New Haven Health System and the Yale School of Medicine. Regarding additional data points, CD4 T-cell counts for HIV patients and Charlson comorbidity index scores for the date of discharge were obtained using ICD-10 codes.

Demographic data for each patient included 1) age at the first hospital admission, 2) sex (male), 3) name of hospital (BH or YNHH), 4) length of stay (calculated by finding difference between date of admission and date of discharge), 5) high-risk antibiotic therapy (binary), 6) PPI therapy (binary), 7) H2A therapy (binary), 8) days of piperacillin/tazobactam, cefepime, or ceftazidime therapy, and 9) Charlson comorbidity index scores upon patient discharge. The electronic Charlson comorbidity index was generated by YNHHS and utilized based on the original and updated indexes.[36,37] The primary exposure variables included days of piperacillin/tazobactam therapy, days of cefepime therapy, and days of ceftazidime therapy. The primary outcome variable assessed was the diagnosis of HA-CDI.

Statistical Analysis

Demographic data was compiled using Microsoft Excel (Office 16) and segregated by individual group at BH and YNHH. Regarding CDI outcomes, the null (not tested) and negative tests were grouped together for subsequent analysis. As the chief measure of the study was the risk of acquiring CDI dependent on antibiotic exposure, null and negative results were grouped as "not acquiring" CDI. Another justification for performing the groupings in this manner was due to feedback from attending physicians and hospital epidemiologists in terms of determining the appropriateness for testing. Microsoft Excel was also used to determine the distributions of

the continuous covariates to guide further analysis. Chi-squared tests were used to determine statistical significance between the covariates in the demographic tables.

Survival analysis was performed using Minitab Version 18 (© 2019 Minitab, LLC, State College, PA) to measure the proportion of individuals with disease survival by days of antibiotic therapy. Survival analysis was performed for both BH and YNHH, directly comparing each cohort group with regards to CDI risk. The survival plots censored patients at hospital discharge after which they could no longer be closely observed for CDI risk.

The multivariate logistic regression models were constructed using Minitab to measure the confounding association between the proportion of individuals with a positive CDI diagnosis and the multiple confounding variables listed. The regression models were separated by binary and continuous confounding variables. The binary covariates consisted of high-risk antibiotic therapy, PPI therapy, H2A therapy, and the male sex. The continuous covariates consisted of Charlson comorbidity index scores, age, and length of hospital admission. Similar to the logic in the survival analysis, these models were separated by each hospital to compare both cohorts. These models were divided into two main areas: one unadjusted model and one adjusted mode using the method of backwards elimination. Statistical significance was determined by using a p-value of < 0.05.

Results

In the 5-year study period, there were a total of 11,909 eligible patients in the total study population. There were 3,666 eligible patients included from BH. 946 were in the piperacillin/tazobactam group, and 2,720 were in the cefepime group (Table 1). The BH cefepime group had a higher average age upon admission than the BH piperacillin/tazobactam group, and the ages for both groups were normally distributed. The BH piperacillin/tazobactam group (53.9%) had a slightly higher proportion of male patients than the BH cefepime group (49.8%) (p = 0.029). The BH cefepime group (58.2%) had more frequent PPI use than the BH piperacillin/tazobactam group (46.7%) (p < 0.001). The BH cefepime group (71.6%) had more frequent H2A use than the BH piperacillin/tazobactam group as well (49.6%) (p < 0.001). Although the BH piperacillin/tazobactam group had a higher average duration of hospital admission than the BH cefepime group, both groups had similar Charlson comorbidity index scores. Both the average duration of hospital admission and Charlson comorbidity index scores were not normally distributed, in which most values fell below the reported means in Table 1. The BH piperacillin/tazobactam group (12.9%) was tested for CDI more frequently than the BH cefepime group (5.8%) (p < 0.001). The rate of positive *C. difficile* tests did not differ between both groups.

According to survival analysis, the BH cefepime group displayed a slightly higher risk for incident CDI (Figure 1). The curve for the BH cefepime group begins to sharply shift downwards around the 13-14 days of therapy mark (Figure 1). However, this discrepancy was not supported by statistical significance (p = 0.127).

The CDI risk for each group was further broken down to account for potential confounders that may explain the observed discrepancies. In the BH piperacillin/tazobactam

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group, high-risk antibiotic use and patients' Charlson comorbidity index scores (higher) were associated with a higher CDI risk in the adjusted model using backwards elimination (OR = 6.066 and OR = 1.247, respectively) (Table 2). In the adjusted model for the BH cefepime group, H2A use was associated with a lower CDI risk, in which the odds ratio was 0.426 ($p = 0.038$). Longer duration of hospital admission was associated with a higher CDI risk, in which the odds ratio was 1.040 ($p = 0.012$) (Table 3).

There were 8,243 eligible patients included from YNHH. 5,239 were in the piperacillin/tazobactam group, and 3,004 were in the ceftazidime group (Table 4). The YNHH piperacillin/tazobactam and YNHH ceftazidime groups had similar average ages upon admission, and the ages were normally distributed. The YNHH piperacillin/tazobactam group (58.7%) had a higher proportion of male patients than the YNHH ceftazidime group (53.3%) ($p < 0.001$). The YNHH piperacillin/tazobactam group (61.0%) had more frequent high-risk antibiotic use than the YNHH ceftazidime group (58.3%) ($p = 0.020$). The YNHH piperacillin/tazobactam group (47.0%) had more frequent PPI use than the YNHH ceftazidime group (44.1%) ($p = 0.011$). The average duration of hospital admission and Charlson comorbidity index scores were similar for both groups. Both data points were not normally distributed in that most values fell below the means reported in Table 4. The YNHH piperacillin/tazobactam group was tested for *C. difficile* more frequently than the YNHH ceftazidime group ($p < 0.001$). The YNHH piperacillin/tazobactam group (0.8%) also had a slightly higher rate of positive *C. difficile* tests than the YNHH ceftazidime group (0.4%) ($p = 0.036$).

According to survival analysis, the YNHH ceftazidime group was associated with a higher CDI risk than the YNHH piperacillin/tazobactam group ($p = 0.016$) (Figure 2). At the 11-

12 mark of days of therapy, the curve for the YNHH piperacillin/tazobactam group began to shift downwards below that of the ceftazidime group.

To further explore the observed discrepancies, the CDI risk for each group was broken down to account for possible confounders. In the YNHH piperacillin/tazobactam group, H2A use and patients' Charlson comorbidity index scores (lower) were found to be associated with a lower CDI risk in the adjusted model by utilizing the backwards elimination method (OR = 0.497 and OR = 0.848, respectively) (Table 5). A longer duration of hospital admission was associated with a higher CDI risk in the adjusted model (OR = 1.038). In the YNHH ceftazidime group, a patient's age (higher) and duration of hospital admission (longer) were found to be associated with an increased CDI risk in the adjusted model (OR = 1.043 and OR = 1.046, respectively) (Table 6). PPI use in the YNHH ceftazidime group was shown to be associated with a lower CDI risk (OR = 0.253).

Discussion

In the BH cohort, there was no significant difference in CDI risk between piperacillin/tazobactam and cefepime as displayed in Figure 1. As a result, this fails to reject the null hypothesis of the CDI risk being the same between penicillin and cephalosporin drugs.

As illustrated in Table 2, patients in the BH piperacillin/tazobactam group receiving high-risk antibiotic therapy (in addition to piperacillin/tazobactam therapy) had 6.066 times the odds of developing CDI than patients not receiving high-risk antibiotic therapy. These odds align well with existing literature, which have displayed an extremely wide range of odds ratios from 1.31 to 49.09.[25,26,38] Patients in the BH piperacillin/tazobactam group with a higher Charlson comorbidity index score were shown to have slightly higher odds of developing CDI than patients with a lower score. Current literature postulates that certain patients such as those with CDI typically have slightly higher Charlson comorbidity index scores than those without CDI, in which odds ratios range from 1.150 to 1.265.[39,40,41]

Table 3 indicates that patients in the BH cefepime group with a longer duration of hospital admission had slightly higher odds of developing CDI than those with a shorter length of stay. A longer length of stay is hypothesized to provide a prolonged medium for a patient to be exposed to *C. difficile*. Events such as requiring antibiotic therapy due to developing an infection or being in close proximity to other patients with *C. difficile* may contribute to the link between longer length of stay and CDI risk.

Table 3 showed that patients in the cefepime group receiving H2A therapy (in addition to cefepime therapy) had 0.426 times the odds of developing CDI than those who did not. H2As are prescribed to patients who exhibit symptoms of conditions such as gastroesophageal reflux disease (GERD), peptic ulcers, or *Helicobacter pylori* infection.[42] H2A use is intended for gastric

acid suppression, though this is hypothesized to introduce favorable conditions for *C. difficile* proliferation.[43] Several studies demonstrate that H2A is a risk factor for CDI, in which the odds ratios range from 1.06 to 3.00.[43] However, other studies have shown inconsistent data in which H2As may have an odds ratio as low as 0.490 to one as high as 3.10.[44] Further study may be required to further explore the complex relationship between CDI risk and H2A use.

In the YNHH cohort, there was a higher CDI risk among the piperacillin/tazobactam group than in the ceftazidime group as shown in Figure 2. Since this difference was supported by statistical significance, it results in a rejection of the null hypothesis that penicillin and cephalosporin drugs are associated with an equivalent CDI risk.

As displayed in Table 5, patients in the YNHH piperacillin/tazobactam cohort receiving H2A therapy (in addition to piperacillin/tazobactam therapy) had 0.497 times the odds of developing CDI as compared to patients who were not receiving H2A therapy. Similar to the findings in Table 3, this further falls in line with inconsistent data surrounding H2A use and CDI risk. Further study may be needed to evaluate H2A therapy based on distribution of its use. Patients in the piperacillin/tazobactam group with higher Charlson comorbidity index scores were found to have lower odds of developing CDI than patients with lower scores. Contrasting with findings in Table 3, it is possible that other covariates may have played a more significant role in confounding CDI risk associated with piperacillin/tazobactam therapy at YNHH. The odds ratio of 0.855 is not significantly lower than the 1.0 mark, so it is possible that other variables may have played a more significant role in confounding CDI risk. Another reason to suggest additional confounding is the findings' contrast with existing literature regarding the direct association between Charlson comorbidity index scores and CDI risk. A longer duration of hospital admission was found to have an almost negligible increase in CDI risk as well.

Patients of an older age and increased duration of hospital admission in the YNHH ceftazidime group had a slightly higher odds of developing CDI as shown in Table 6. Older age may increase CDI risk due to age-related impairment of the immune system, higher antibiotic utilization, and more frequent healthcare exposure.[45,46] However, some studies also indicate a small magnitude of the documented risk, which is demonstrated by the odds ratio of 1.045 in Table 6.[47] PPI use in the YNHH ceftazidime was conversely shown to have a low odds ratio of 0.253 with regards to CDI risk (Table 6). Although the confidence interval had a wide range, this finding contrasts current literature depicting the association between PPI use and CDI risk. Consistent with the proposed mechanisms for H2A use being associated with a higher CDI risk, the stomach acid suppression induced by PPI use has been shown to introduce environmental conditions favorable for *C. difficile* proliferation.[48] Many studies demonstrate a relatively high risk of acquiring principal and recurrent CDI following prolonged PPI use.[49] Several studies have shown odds ratios ranging from 0.8 to 18.1 with regards to developing CDI.[50] There are some contrasting studies showing lower corresponding odds ratios ranging from 0.4 to 0.8.[48] Further study may be required to evaluate the other binary covariates to more closely examine the association with PPI use. Another potential hypothesis to explain the documented low odds of CDI risk associated with PPI use is a distribution of days of therapy and distribution of use. It is possible that due to the strong acid suppression capabilities of PPIs, they are used in more critically ill patient populations such as those admitted to intensive care units. A closer examination may focus on the distribution of PPI use by hospital site or days of therapy to better assess severity of acute disease. These analyses may further explain the depicted inverse association between PPI use and CDI risk.

The higher CDI risk associated with piperacillin/tazobactam at YNHH brings about questions of imposing any restrictions on the formulary. As this study has shown a higher CDI risk associated with its empiric prescription, the two key remaining factors to consider are risk factors for HAIs and the cost. As stated in the literature, piperacillin/tazobactam has excellent coverage against Gram-positive, Gram-negative, and anaerobic bacteria. Ceftazidime is primarily reserved for use against Gram-negative bacteria such as *Pseudomonas aeruginosa*.[31] One study directly compared the use of piperacillin/tazobactam and broad-spectrum cephalosporins with evaluating the risk for HAIs caused by drug-resistant *Enterobacter spp.*, in which cephalosporin therapy led to a higher risk of infection.[51] Another study determined that piperacillin/tazobactam and broad-spectrum cephalosporins were associated with similar CDI risks for developing intra-abdominal infections, bloodstream infections, and urinary tract infections caused by Gram-negative bacteria.[52] While the costs and risk for HAIs caused by Gram-negative bacteria are similar between both antibiotics, the factor that may recommend against a YNHH formulary change is piperacillin/tazobactam's extended coverage against common Gram-positive and anaerobic bacteria which may be needed in some clinical circumstances.

Although no difference in CDI risk between piperacillin/tazobactam and cefepime was observed in the BH cohort, cefepime and ceftazidime share structural and procedural similarities as they are both β-lactam antibiotics in the cephalosporin class. Furthermore, there is some evidence showing provider preference for cefepime over ceftazidime as anti-pseudomonal agents.[53] Some data supports this assertion by showing lower drug resistance among pneumonia patients and less incident vancomycin-resistant *Enterococcus* (VRE) among cefepime treatment groups compared to those with ceftazidime.[54] However, clinical outcomes for pneumonia did not considerably differ between the cefepime and ceftazidime treatment groups in the study.[54]

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Cefepime's added Gram-positive coverage may warrant additional study to compare the CDI risk between penicillin and cephalosporin drugs. The current findings may indicate that cefepime has a similar impact on altering the commensal gut flora as piperacillin/tazobactam, accounting for a similar CDI risk. In the YNHH cohort, the findings indicate that ceftazidime may not significantly alter the composition of the commensal gut flora, explaining the lower CDI risk. Despite a recommendation against a formulary change at YNHH, the discrepancy in CDI risk between piperacillin/tazobactam and ceftazidime may justify further action given the rising trend of CDI incidence. The observed discrepancy may lead to further investigation into the possibility of favoring ceftazidime for empiric Gram-negative coverage when Gram-positive and anaerobic coverage are not warranted.

An alternative explanation to address the discrepancy in CDI risk between piperacillin/tazobactam and ceftazidime may be attributed to an inherently higher overall degree of utilization of piperacillin/tazobactam relative to ceftazidime.[55] Due to its broader coverage, utilization of piperacillin/tazobactam is significantly higher and can span a wider patient population including multiple subsets with higher risks for developing CDI.

One study measured trends in antibiotic use among an alliance of US hospitals between 2002 and 2006, in which the researchers found an 84% increase in piperacillin/tazobactam over the 5-year study period.[56] This significant increase occurred despite sporadic national piperacillin/tazobactam shortages, indicating that the rate of increase could potentially accelerate as the shortage alleviated. During this study period, piperacillin/tazobactam was the third most commonly prescribed antibiotic within the focused network of hospitals behind vancomycin and cefazolin.[56] As the rate of prescribing has increased in recent years, additional studies evaluate appropriate use of the antibiotic based on empiric indication. Two studies conducted such an

evaluation, in which one study determined that piperacillin/tazobactam was used "inappropriately" 17% of the time compared to 7% of the time for vancomycin. Another study determined that in four hospitals, piperacillin/tazobactam was inappropriately used 28.5% of the time.[57,58] In this study, piperacillin/tazobactam utilization may have differed by hospital to explain the observed discrepancies.

The YNHH piperacillin/tazobactam group was also tested for CDI more frequently than the YNHH ceftazidime group. One potential explanation for this finding is that piperacillin/tazobactam may have been prescribed more frequently in critical care patients compared to ceftazidime. As a result, patients prescribed piperacillin/tazobactam may have had an inherently higher risk for developing CDI, leading to more frequent testing and more positive CDI cases. It is possible that the positive results in the YNHH piperacillin/tazobactam group may be reflective of *C. difficile* colonization rather than true infection. Colonization is either symptomatic or asymptomatic. Symptomatic colonization is associated with signs of diarrhea, whereas asymptomatic colonization is the detection of *C. difficile* in the absence of diarrhea.[59] If the positive test results reflected colonization, this may not support the assertion that piperacillin/tazobactam is necessarily associated with its depicted risk. Some studies have shown that 1-4% of healthcare workers in the US may be asymptomatically colonized with *C. difficile*, whereas 7-15% of non-healthcare workers outside the US may be asymptomatically colonized with *C. difficile*.[60,61]

A potential implication of the more frequent testing among the YNHH piperacillin/tazobactam group may indicate that piperacillin/tazobactam poses a greater risk for antibiotic-associated diarrhea. Diarrhea is a common adverse event associated with antibiotic therapy. One study shows that antibiotic-associated diarrhea occurs in 5-30% of patients either

shortly after initiating antibiotic therapy or up to two months following the conclusion of treatment.[62] While there is variation in the prevalence of antibiotic-associated diarrhea with different antibiotic classes, current literature has shown significant associations between antibiotic-associated diarrhea and piperacillin/tazobactam therapy.[63,64] This potential link may distinguish between the risk of *C. difficile* colonization or true infection associated with piperacillin/tazobactam. *C. difficile* is known to be a major contributor to antibiotic-associated diarrhea, in which 10-25% of antibiotic-associated diarrhea cases are attributed to the anaerobic bacterium.[62] Future study may explore this distribution of penicillin and cephalosporin drugs by site of care to lend an explanation for the differences in *C. difficile* testing patterns. As such discrepancies in antibiotic utilization are observed, the focus shifts to optimal antibiotic stewardship.

Several strategies have been implemented to de-escalate antibiotic use including bolstering facility-wide educational programs and setting new standards for selection of an appropriate agent, route of administration, dose, and duration of therapy.[65] One strategy used to combat high utilization of antibiotics is the implementation of a "time-out"[3] in a hospital's electronic medical record.[66] A team at a tertiary care hospital implemented a 72-hour time-out for piperacillin/tazobactam, which involved installing a "stop" in the electronic medical system for empiric piperacillin/tazobactam orders for patients lacking positive cultures. The team noted a significant decrease in the duration of empiric use, inappropriate dosing, and an increase in the rate of antibiotic de-escalation.[67] In the case that higher piperacillin/tazobactam utilization

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[3] Antibiotic time-out – an intervention prompting the reassessment of the continuing need and choice of antibiotics when the clinical picture is clearer and more diagnostic information is available.

contributed to the difference in CDI risk compared to ceftazidime, it may warrant further exploration into antibiotic de-escalation interventions.

Alternatively, one tertiary care hospital implemented an antibiotic stewardship program aiming to decrease overall cephalosporin use in terms of recommended daily doses (RDD) per 100 patient days.[68] While third-generation cephalosporin use decreased from 16.3 RDD per 100 patient days to 10.3 RDD per 100 patient days, it also led to penicillin use increasing from 15.4 RDD per 100 patient days to 18.2 RDD per 100 patient days.[68] Another study followed a similar antibiotic stewardship program structure and observed an overall decrease in third-generation cephalosporin use from 34 RDD per 100 patient days to 11 RDD per 100 patient days.[69] The program also led to a ten-fold increase in penicillin use.[69] While current literature postulates that penicillin drugs may be preferable with regard to lowering CDI risk compared to cephalosporin drugs, the impact of cephalosporin de-escalation may also increase penicillin utilization to the point of potentially raising CDI risk. Along with a closer examination for piperacillin/tazobactam de-escalation in particular clinical situations, it may be worthwhile to perform a similar examination for cephalosporin de-escalation. Further study may explore the relationship between the utilization of cephalosporin drugs and penicillin drugs, particularly following the implementation of an antibiotic stewardship program focusing on either antibiotic class. To work towards achieving optimal antibiotic stewardship, the associated costs with each antibiotic class may also be an area of additional study, as utilization of some antibiotic classes have been shown to incur higher costs than that of others.[70]

Optimal antibiotic stewardship requires efforts in both the hospital and community. CDC analysis revealed a slight downwards trend in outpatient antibiotic prescribing from 877 prescriptions per 1,000 persons in 2010 to 835 prescriptions per 1,000 persons in 2014.[71]

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However, this rate slightly increased in 2015 to 838 prescriptions per 1,000 persons in 2015.[71] While this increase may be viewed as minor, researchers found that at least 30% of the included outpatient antibiotic prescriptions were deemed "unnecessary". This shift is noticeably worse among the elderly population, who concurrently are at a higher risk for CDI than the younger demographic. Following a similar trend as in the CDC analysis, a team of researchers measured a steady decline in outpatient antibiotic prescriptions in the elderly from 1,364 claims per 1,000 beneficiaries in 2010 to 1,309 claims per 1,000 beneficiaries in 2014.[72] This rate, however, rose to 1,364 claims per 1,000 beneficiaries in 2015. Current literature has shown an increase in incident CDI in the community, in part due to excessive antibiotic use in the outpatient setting. While the interaction between CA-CDI and HA-CDI is not fully understood, many researchers agree on the presence of an association to some degree.[73,74] As more individuals are hospitalized due to CDI, the likelihood of shedding the pathogen into the hospital environment increases. While reducing CDI incidence requires a litany of interventions spanning hand hygiene, environmental cleaning, and diagnostic stewardship, antibiotic stewardship addresses the principal risk factor for CDI cases.

This study has several limitations. First, no inter-facility or aggregate (piperacillin/tazobactam versus third/fourth-generation cephalosporin) comparison was made between BH and YNHH to evaluate comparative CDI risk associated with empiric antibiotic therapy. This was primarily due to the differing *C. difficile* assays used at each hospital (See Appendix 2), variation in provider preferences, and subsequent complexities with assay standardization. An inter-facility comparison may provide more robust clinical data to support any decisions concerning a change to the existing formulary. Further study may revolve around such an aggregate comparison due to similarities in the patient populations at BH and YNHH.

Second, the composition of inpatients has shifted over the 5-year study duration at BH and YNHH. Due to the exclusion criteria by inpatient unit, it is possible that eligible patients such as those in general medicine were excluded as a result of being admitted to an excluded unit. Conversely, it is possible that ineligible patients such as those in hematology-oncology were included due to being admitted to a general medicine unit.

Third, patients were included based on the first hospital admission falling under the inclusion criteria. Many patients had multiple hospital admissions in which there was a possibility of a CDI diagnosis in a subsequent hospitalization. However, since all patient data from the first eligible admission was used, some CDI cases may have been missed despite potentially being linked to antibiotic use.

Fourth, the antibiotic confounders were restricted to select antibiotics known to be high-risk. Based on current literature, cephalosporins, clindamycin, fluoroquinolones, and carbapenems have been associated with high CDI risk. Specific antibiotics were included based on the drugs available on the BH and YNHH formularies. While most studies conclude that there is a low CDI risk associated with tetracyclines, some show a moderate CDI risk associated with additional penicillin drugs and macrolides.[25,26] In some cases, macrolides have shown to have an odds ratio of 5.2 of developing CDI with the BI/NAP1/027 strain and a relative risk of 1.30 when evaluating patients with penicillin allergies.[75,76,77] The BI/NAP1/027 strain, first isolated in North America, has gained attention due to its propensity to cause severe outbreaks with unexpectedly high mortality.[77] Due to the significantly high virulence, it has been hypothesized that the BI/NAP1/027 strain may be associated with additional or different risk factors commonly associated with other strains.[77] As a result, macrolides and other moderate-risk antibiotics become of more importance when evaluating CDI risk with antibiotic use for more novel strains.

Although the data evaluating CDI risk with macrolide therapy is inconsistent, this category was excluded from the high-risk classification. One cannot rule out its status as a confounder, particularly if it is preferred for a patient population with allergies to penicillin drugs such as piperacillin/tazobactam.

Fifth, Charlson comorbidity index scores were solely available at the time of patient discharge. As a Charlson comorbidity index score may change throughout a patient's visit, the recorded scores may be higher or lower than that present upon admission. Additionally, these scores measure the likelihood of a patient's death over the course of the next six months; they do not measure the acute severity of disease. Although Charlson comorbidity index scores were reported to be similar across the studied cohorts, they do not measure severity of disease which may have explained discrepancies in *C. difficile* testing patterns.

Next steps will focus on evaluating an aggregate comparison of CDI risk between piperacillin/tazobactam and third/fourth-generation cephalosporin drugs. A statistical consult may be sought for optimal standardization of facility-level differences (provider preference, patient demographics, *C. difficile* testing patterns) between both hospitals. These aggregate findings may shed more insight into comparative CDI risk between antibiotics and explain the discrepancies in associated CDI risk observed in both hospitals studied.

Another next step may be a deeper level of analysis evaluating the impact of covariates such as PPI and H2A use on CDI risk. Due to the fact that some continuous covariates are not normally distributed, stratification or categorization may be needed for a more robust mode of confounding analysis. An example of further risk stratification could be examining piperacillin/tazobactam, cefepime, or ceftazidime therapy by site of care to address potential confounding with their distributions of use. Addressing existing limitations such as parsing out

those who received empiric antibiotic therapy following a *C. difficile* test may be a priority. Primary exposure variables such as days of therapy can be further broken down into categories to allow for a closer look on the specific time point(s) in which the CDI risk of one antibiotic began separating from that of the other. Another possibility is to incorporate other modes of bivariate and multivariate analysis to further explore the complex relationships between CDI risk and the individual covariates.

Overall, the relationships between CDI risk and empiric antibiotic use in this study reflect the variation observed in current literature. Piperacillin/tazobactam at YNHH was shown to have a higher CDI risk than ceftazidime, whereas no difference in CDI risk between piperacillin/tazobactam and cefepime at BH was observed. These results contrasted the hypotheses based on existing literature, warranting a closer look in sources of variation in CDI risk between the antibiotics in question. Additional study may be needed to further stratify the CDI risk associated with individual antibiotics within a class and explore various interventions to improve antibiotic stewardship efforts.

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Appendix

<u>Appendix 1: CDC NHSN LabID for *Clostridioides difficile*</u>

According to The Centers for Disease Control and Prevention, an individual must meet at least one of the following criteria to be infected with *C. difficile*:

1) Positive test for toxin-producing *C. difficile* on an unformed stool specimen (conforms to the shape of the container).

2) Patient has evidence of pseudomembranous colitis on gross anatomic (includes endoscopic exams) or histopathologic exam.

<u>Appendix 2: *C. difficile* assays for BH and YNHH</u>

Bridgeport Hospital Testing Algorithm:

If GDH/Rapid Toxin assay result: Negative/Negative → No CDI
If GDH/Rapid Toxin assay result: Positive/Positive → CDI present
If GDH/Rapid Toxin assay result: Discordant → PCR required
      If PCR result: Positive → CDI present
      If PCR result: Negative → No CDI

YNHH Testing Algorithm:

If GDH/Rapid Toxin assay result: Negative/Negative → No CDI
If GDH/Rapid Toxin assay result: Positive/Positive → CDI present
If GDH/Rapid Toxin assay result: Discordant → Cytotoxin Neutralization Assay required
      If Cytotoxin Neutralization Assay result: Positive → CDI present
      If Cytotoxin Neutralization Assay result: Negative → No CDI