Clostridium difficile Infection Outcome Stratified by Severity:

A Comparison of Three Indices

BY

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THESIS

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LIST OF ABBREVIATIONS

APIC	Association for Professionals in Infection Control and Epidemiology
AUC	Area Under the Curve
CDI	*Clostridium difficile, C. difficile*
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CDI	*C. difficile* Infection
EIA	Enzyme Immunoassay Kit
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ICU	Intensive Care Unit
IV	Intravenous
PMC	Pseudomembranous Colitis
PO	Oral
SCT	Severity Index-Concordant Therapy
SDT	Severity Index-Discordant Therapy
SHEA/IDSA	Society for Healthcare Epidemiology in America and Infectious Diseases Society of America
SrCr	Serum Creatinine
UIHHSS	University of Illinois Hospital & Health Sciences System
WBC	White Blood Cell

SUMMARY

Clostridium difficile infection (CDI) is the leading cause of hospital-acquired infection. This colonic infection is responsible for approximately $5 billion dollars in excess healthcare costs per year in the U.S. The severity of CDI dictates both treatment options and prognosis. Depending on the severity of illness, patients can experience a spectrum of *C. difficile*-associated diseases including diarrhea, toxic megacolon, colon perforation, or death. Stratifying anti-CDI therapy based on severity has been shown to improve clinical outcomes. According to the Society for Healthcare Epidemiology in America and Infectious Diseases Society of America (SHEA/IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines, severe infections should be treated with vancomycin and non-severe treated with metronidazole.

While several severity indices exist to differentiate between severe and non-severe CDI, it is unclear which index predicts the best clinical outcome. Moreover, there are significant discrepancies between severity indices and guidelines including treatment recommendations. This heterogeneity limits the practice of standardized, evidence-based medicine and may negatively impact patient care. This retrospective study compared SHEA/IDSA, ESCMID, and Zar's severity indices to determine the index with the best prognostic value. While the SHEA/IDSA and ESCMID are standard guidelines against CDI, Zar's index was University of Illinois Hospital & Health Sciences Systems'(UIHHSS) guideline against CDI during the study period.

Each CDI case was classified as either severity index-concordant (SCT) or discordant (SDT) depending on the severity classification and treatment received according to the aforementioned severity indices. As the primary end point, the study assessed which

index reduced the risk of poor outcome most significantly. Poor outcome was classified as recurrent infection, treatment failure, or 30-day mortality post CDI diagnosis. In addition, the effects of concordance on length of stay (LOS) post CDI diagnosis as well as differences in outcome between vancomycin and metronidazole were assessed.

Out of the 229 CDI cases evaluated, 31% experienced poor outcome. Incidence of severe CDI ranged between 28% and 97% depending on the severity index used. After adjusting for variables, concordance to SHEA/IDSA, ESCMID, and Zar severity indices reduced the odds of poor outcome by 60%, 49%, and 66%. However, only SHEA/IDSA index produced a statistically significant reduction. Concordance to an index also reduced LOS post diagnosis and cost. After stratifying by CDI severity, there was no significant difference in the risk of poor outcome between metronidazole and vancomycin monotherapy groups. However, the incidence of poor outcome was higher in the metronidazole monotherapy group.

The lack of consistency between guidelines and severity indices can complicate patient therapy and negatively affect clinical outcome. This is the first study to compare the three aforementioned severity indices. Although retrospective and limited in sample size, this study highlights the importance of following evidence-based medicine. Considering the simplicity of SHEA/IDSA's criteria and profound reduction in outcomes, the study found the SHEA/IDSA index to have the best prognostic value.

I. INTRODUCTION

A. Background Information

Clostridium difficile is a Gram-positive, spore-forming, and toxin-producing bacterium that is responsible for causing *C. difficile* infection (CDI) [1–3]. CDI is a colonic infection that primarily develops in patients who are exposed to antibiotics [3]. Antibiotic use disrupt the normal gut microbiota and allows *C. difficile* spores to germinate into their active vegetative state, produce exotoxins, and cause clinical CDI. These toxins mediate an immense inflammatory response in the colon and cause the hallmark symptom of CDI: diarrhea.

Currently, CDI is the leading cause of nosocomial infection in the U.S. [1,2] and associated with increased cost and length of stay (LOS) per admission [4–6]. Due to the significant associated morbidity and mortality associated, the Centers for Disease Control and Prevention (CDC) has classified CDI as an "urgent public threat" that requires immediate attention [1,7]. Despite increased awareness in diagnosing and treating CDI, the morbidity, mortality, and cost associated with this infection continues to rise [2,5,8]. Recent studies indicate CDI's burden on acute care facilities in the U.S. to be as much as $4.8 billion per year [2].

CDI is primarily diagnosed by identifying its toxins in stool samples [9]. Although there are several methods to diagnose CDI, the two common detection methods are using enzyme immunoassay (EIA) kits and polymerase chain reaction (PCR) technology. Although PCRs have higher sensitivity and specificity, the low cost, rapid turnaround time (~1 hour), and ease of adaptability made EIAs highly appealing. According to Society for Healthcare Epidemiology in America and Infectious Diseases Society of

America's (SHEA/IDSA) 2010 guideline, 90% of laboratories were using EIA kits during the time of publication. However, due to recent advancements in toxin detection, guidelines and experts advocate for a more sensitive stool testing method such as PCR technology [1,10]. The clinical relevance of these recommendations has led many institutions to start using PCR instead of EIA including UIHHSS, which switched to PCR technology in May 31, 2011. Of note, UIHHSS's EIA kit, Meridian Premier™ toxin A and B kit, had one of the highest sensitivity and specificity among EIAs with reported values exceeding 91% and >97%, respectively [11–14].

During an episode of CDI, patients can experience mild, moderate, severe, or severe-complicated illness [9,15,16]. The true rates of severe and non-severe CDI are difficult to determine as incidences vary widely based on the criteria used to classify the severity. In one study, the incidence of severe CDI ranged between 23% and 49% depending on the severity criteria used [17]. However, the overall incidence and severity is believed to be on the rise [18,19]. Classifying the severity of illness is clinically imperative as patients experiencing severe infection are at an increased risk of developing CDI-associated complications including renal dysfunction, colonic perforation, sepsis, and death [9]. Treatment recommendations [9,15,16] and risk of recurrent infection [16] also vary based on severity of infection.

B. Significance of the Problem

Previous studies have repeatedly shown that stratifying anti-CDI therapy based on severity improve outcomes [9,15,16]. As such, several published treatment guidelines for CDI including SHEA/IDSA [9], the European Society of Clinical Microbiology and Infectious Diseases (ESCMID [16], and the American Journal of Gastroenterology [20]

recommend the use of metronidazole 500 mg every 8 hours for non-severe CDI episodes and oral (PO) vancomycin 125 mg every 6 hours for severe episodes. It is worth noting that each clinical guideline has a different definition for severity, treatment failure, and recurrent CDI. There is also discrepancy on the management of severe-complicated CDI including the use of combination therapy (PO vancomycin and intravenous [IV] metronidazole) and surgical alternatives. This heterogeneity between the guidelines and severity criteria makes it challenging for clinicians to follow standardized, evidence-based clinical practice during CDI episodes. This may cause delay in recognizing the severity of infection and lead to inappropriate treatment selection as well as unfavorable patient outcome. Thus, promptly identifying the severity of infection and selecting the appropriate treatment is critical to improve the patient's clinical outcome [9,15,16,20–22]. This has been consistently shown in clinical trials [15] and meta-analyses [23]. For instance, a 2015 meta-analysis showed no difference in clinical cure between metronidazole and vancomycin for mild CDI (Odds Ratio [OR] = 0.67, 95% confidence interval [95% CI]: 0.45 to1.00, P=0.05); however, vancomycin was associated with statistically significant higher clinical cure in severe CDI cases (OR = 0.46, 95% CI: 0.26 to 0.80, P=0.006) [23]. It is important to mention that the definition for severity was not universal in the included studies.

C. Study Objective and Significance

Although several different severity indices have been proposed, there is a lack of consensus regarding which severity index best predicts outcome during an episode of CDI [9,15,16,20–22]. There are also limited data that compare severity indices with clinical outcomes as an endpoint [17]. Identifying a severity index that is correlated to a

favorable patient outcome is vital to optimizing anti-CDI therapy and improving clinical outcome. The purpose of this study was to evaluate three severity indices to identify the index with the best prognostic value for patients with CDI.

II. METHODS

A. Study Design

This was a retrospective, single center study conducted at University of Illinois Hospital & Health Sciences System (UIHHSS), a 495-bed tertiary medical center. This study was approved by UIHHSS's institutional review board committee with a waiver of consent granted. Eligible patients were ≥18 years old and receiving IV or PO metronidazole or PO vancomycin for definitive non-recurrent CDI between 2006 and May, 31 2011. Patients with recurrent CDI, defined as a confirmed CDI within 8 weeks after the onset of a previous, successfully treated episode of CDI, were excluded. Thus, patients with previous episodes of CDI which were non-recurrent were still included (TABLE I). Each CDI case was confirmed by testing patients' fecal samples via an EIA kit. Patients receiving concurrent metronidazole or PO vancomycin for other reasons were excluded.

TABLE I
CLASSIFICATIONS OF CDI [23]

Types of Infection	**Definition**
Hospital-onset	Confirmed CDI > 3 days after admission to UIHHSS
Community-onset	Confirmed CDI ≤ 3 days after admission to UIHHSS
Community-onset healthcare facility associated	Confirmed CDI ≤ 3 days after admission to UIHHSS and patient was discharged with non-CDI diagnosis within the previous 4 weeks
Recurrent	Confirmed CDI within 8 weeks after the onset of a previous, successfully treated episode of CDI

B. Rationale Behind Data Collection and Definitions

Pre-specified data were recorded from patient charts via the electronic medical record. Candidate variables were selected based on previous publications to capture patient-specific risk factors for developing CDI [9,15,16,21]. These included demographics, laboratory values, comorbidities, concurrent medications as well as other factors such as ICU admission, intubation, and receiving tube feeding or total parenteral nutrition.

All laboratory values were collected within 24 hours from the date of CDI diagnosis, which was defined as the first day of initiating CDI therapy. Baseline white blood cell (WBC) count and serum creatinine (SrCr) were collected 3 days prior to CDI diagnosis. In cases where WBC count and SrCr were not available 3 days before CDI diagnosis, the earliest existing value prior to starting CDI therapy was considered baseline. Baseline comorbidities were assessed using the Charlson comorbidity index (CCI) [25]. The CCI incorporates 19 comorbid illnesses to calculate the relative risk of mortality. In this study, patient's CCI during admission was used to control for pre-CDI illnesses. The use of CCI to control for comorbidities in CDI-related research is well-documented [26–29].

Since antibiotics are a significant risk factor for developing CDI [1], a detailed approach was implemented to capture patients' exposures to antibiotics. Based on a preliminary analysis and poster presentation (IPhA Annual Conference, Lombard, IL. September, 2015. Poster number: PIP102), the duration of antibiotic exposure was grouped in to <10, 10-20, or > 20 days. Exposure to antibiotics was further classified into current exposure (antibiotic use from date of admission to date of CDI diagnosis) and prior exposure (antibiotic use within 90 days of admission). Furthermore, a study by

Stevens et al. demonstrated a significant increase in the risk of developing CDI with an increase in the number of exposed antibiotics [30]. As such, the numbers of current and past antibiotics were recorded.

Antibiotics were also classified as “low” or “high” -risk groups based on two meta-analyses that identified a set of antibiotics that significantly increased the likelihood of patients developing CDI [31,32]. In Brown et al.’s meta-analysis, clindamycin (OR = 16.80; 95% CI, 7.48 to 37.76), fluoroquinolones (OR = 5.50; 95% CI, 4.26 to 7.11), cephalosporins, monobactams, and carbapenems (OR = 5.68; 95% CI, 2.12 to 15.23), as well as macrolides (OR = 2.65; 95% CI, 1.92 to 3.64), sulfonamides/trimethoprim (OR = 1.81; 95% CI, 1.34 to 2.43), and penicillins (OR = 2.71; 95% CI, 1.75 to 4.21) were significantly associated with developing community-onset CDI [31]. In Silmings and Riley’s meta-analysis, third-generation cephalosporins (OR = 3.20; 95% CI, 1.80 to 5.71), clindamycin (2.86; 95% CI, 2.04 to 4.02), second-generation cephalosporins (OR = 2.23; 95% CI, 1.47 to 3.37), fourth-generation cephalosporins (OR = 2.14; 95% CI, 1.30 to 3.52), carbapenems (OR = 1.84; 95% CI, 1.26 to 2.68), sulfamethoxazole/trimethoprim (OR = 1.78; 95% CI, 1.04 to 3.05), fluoroquinolones (OR = 1.66, 1.17 to 2.35), and penicillin combinations (OR = 1.45; 95% CI, 1.05 to 2.02) were significantly associated with developing hospital-onset CDI [32]. Since this study comprised of community- and hospital- acquired CDI, the aforementioned antibiotics were classified as “high-risk” antibiotics. Other antibiotics were categorized as “low-risk.” In cases when patients concurrently received “high”- and “low”- risk antibiotics, patients were recorded as receiving “high-risk” antibiotics.

In addition to antibiotic exposure, hospitalization also increases the risk of developing

CDI [33]. However, the incidence of community-acquired CDI has been increasing in populations without the traditional risk factors such as exposure to antibiotics or hospitalizations [2,28]. Accordingly, this study implemented the Association for Professionals in Infection Control and Epidemiologys' (APIC) definitions to differentiate between hospital-onset, community-onset, and community-onset healthcare facility associated CDIs as well as recurrent CDI (TABLE I) [24]. This organization is dedicated to prevent infection and it adapted the classifications of CDI from the CDC [34]. It is important to mention that there is no consensus on the classification of CDI among agencies. For instance, while SHEA/IDSA's 2010 guideline [9] considers 48 hours the dividing time point between community- and hospital- onset CDI, APIC [24] and CDC[34] consider 72 hours. Moreover, apart from clinical experience, there is no clear rationale behind each agency's method of categorizing CDI in their respective manner. Regardless, identifying this information can inform epidemiologists and healthcare facilities the origin of the infection and possibly aid in controlling the source of the infection.

C. Outcome Measure

The primary aim of the study was to identify the CDI severity index that had the best prognostic value. To do so, the incidence of poor outcome in the severity index-concordant therapy (SCT) group and severity index-discordant therapy (SDT) group was calculated and stratified by each severity index. Poor outcome was defined as recurrent CDI (confirmed CDI within 8 weeks after the onset of a previous, successfully treated episode of CDI), treatment failure (requiring treatment modification while on active CDI therapy due to no clinical improvement), or 30-day all-cause mortality from date of CDI

diagnosis (identified via Social Security Death Index, if prior to 30 days discharged). There are no universally adapted definitions for poor outcome, treatment failure, or recurrent CDI exist currently. In this study, the endpoints were chosen due to their clinical relevance, expert opinion, and use in other studies [35]. The index with the lowest incidence of poor outcome in the SCT was considered to have the best prognostic value.

Severity was assessed according to the three severity indices (TABLE II) [9,15,16]. Treatment options were evaluated according to the previously mentioned therapies recommended by ESCMID [16], SHEA/IDSA [9], and the American Journal of Gastroenterology [20]. As such, a case of SCT was defined as a severe CDI case treated with vancomycin 125 mg every 6 hours or a non-severe CDI case treated with metronidazole 500 mg every 8 hours. All other treatments were classified as SDT. Combination therapy with IV metronidazole and PO vancomycin is recommended in the above-mentioned guidelines for cases of severe-complicated CDI as defined by shock, ileus, or toxic megacolon. As these symptoms could not be assessed accurately retrospectively, patients who received this regimen were considered as SDT as well.

TABLE II
DEFINITIONS OF SEVERE CDI PER SEVERITY INDEX

Diagnostic variables	**SHEA/IDSA Guideline**	**ESCMID Guideline**	**Zar Criteria (points)**
Age	-	≥ 65	> 60 (1)
Temperature (^{0}C)	-	> 38.5	> 38.3 (1)
WBC[a](1000 cells/mm^3)	≥ 15	≥ 15	> 15 (1)
SrCr [b] (mg/dL)	≥ 1.5xbaseline	≥ 1.5 or ≥1.5xbaseline	-
Albumin (mg/dL)	-	<3	< 2.5 (1)
Comorbidities	-	Presence of comorbidities[c]	-
Others	-	Colonoscopy/imaging	PMC[d] or ICU stay (2)

[a]WBC = white blood cell

[b]SrCr = serum creatinine

[c]Refer to Debast et al. for the full list of comorbidities [16]

[d]PMC = pseudomembranous colitis

SHEA/IDSA [9]: severe CDI is diagnosed with the presence of any of the listed variables
Zar [15]: severe CDI is diagnosed when there is a cumulative point total of ≥ 2 points
ESCMID [16]: severe CDI is diagnosed with the presence of any of the listed variables

There are several reasons for this study to compare the aforementioned three severity indices. The study by Zar et al. was the first prospective, randomized controlled study to stratify and treat CDI according to severity of illness [15]. According to Zar et al., the severity assessment score was developed based on investigators' clinical experiences (Zar 2015, personal communication). Moreover, Zar's severity criteria were UIHHSS's guideline for the treatment of CDI during this study period (2006 – 2011). Conversely, SHEA/IDSA and ESCMID severity indices are internationally recognized guidelines designed to guide clinical practice [9,16]. While SHEA/IDSA serves as the U.S.'s national guideline against CDI, ESCMID is the leading agency in recommending strategies to diagnose and treat infectious disease in Europe. Their severity indices were constructed by incorporating published literature and clinical expertise.

In addition, the effect of concordant therapy may reduce LOS and cost. To truly capture the effect of SCT on LOS, the LOS post CDI diagnosis (length of hospitalization from CDI diagnosis to discharge date) was calculated. The difference in LOS post CDI diagnosis as well as room and boards cost was later calculated for the SCT and SDT groups. Since each CDI case's location was not recorded, UIHHSS's least costly room and boards estimate was used to calculate the costs in the two groups.

The difference in outcome between metronidazole 500 mg every 8 hours monotherapy and oral vancomycin 125 mg every 6 hours monotherapy was also assessed. Additionally, the study evaluated the difference in incidence of poor outcome between combination therapy (vancomycin & metronidazole therapy started together or one therapy option added on to another) and metronidazole-based treatment (metronidazole monotherapy regardless of dose or route). Combination therapy was also compared

against vancomycin-based treatment (vancomycin monotherapy regardless of dose or route and CDI cases that were initially treated with metronidazole, but switched to vancomycin).

D. Statistical Analysis

Shapiro-Wilk test assessed normality. Wilcoxon-Mann-Whitney, Fisher's exact, and t-test were used to assess ordinal, categorical, and continuous variables, respectively. Continuous variables were categorized based on trends observed during previous analysis for a poster presentation (IPhA Annual Conference, Lombard, IL. September, 2015. Poster number: PIP102). For each model, all possible candidate variables were inputted in a multivariable logistic regression. Models were constructed via the backward selection method [36] Variables were retained in the model at a p-value cut-off of 0.05. Clinical judgment, biological plausibility, and previous publications were used to force in variables that may affect the outcome of CDI such as immune status, CCI, age, and LOS pre CDI diagnosis. Patients were considered immunocompromised if they were actively receiving immunosuppressants, antineoplastics, or glucocorticoids greater than or equivalent to 20 mg of prednisone daily for 14 days. Overall, these variables were selected to control for patient's health status before developing CDI. As such, they remained in all models. Variables that are part of the severity criteria were not inputted in the models. Thus, the variable, "age" was removed from the ESCMID and Zar criteria models. Also, LOS pre CDI diagnosis was removed from the models that assessed the effects of concordance on LOS post CDI diagnosis. All constructed multivariable regressions assessed risk of experiencing poor outcome after adjusting for variables.

Goodness-of-fit was assessed via Hosmer-Lemeshow and area under the receiver operating curve (AUC) assessed discriminatory ability of the models [36]. Internal validation was assessed via 10-fold cross-validation technique. Statistical significance was denoted as a 2-tailed P-value<0.05 for all tests. Statistical analysis was performed on the statistical software package Stata 12.0®.

III. RESULTS

A. Patient Selection and Characteristics

Out of the 1,236 screened CDI cases, 229 were included (Figure 1). The majority of patients were excluded due to receiving empiric CDI therapy without a positive EIA result. The median age and CCI were similar across all groups (TABLE III). Cases with poor outcome had significantly longer LOS and LOS post CDI diagnosis than those with favorable outcome ($P<0.05$, TABLE III). The majority of infections were hospital acquired (66%).

Figure 1. Inclusion and Exclusion Criteria

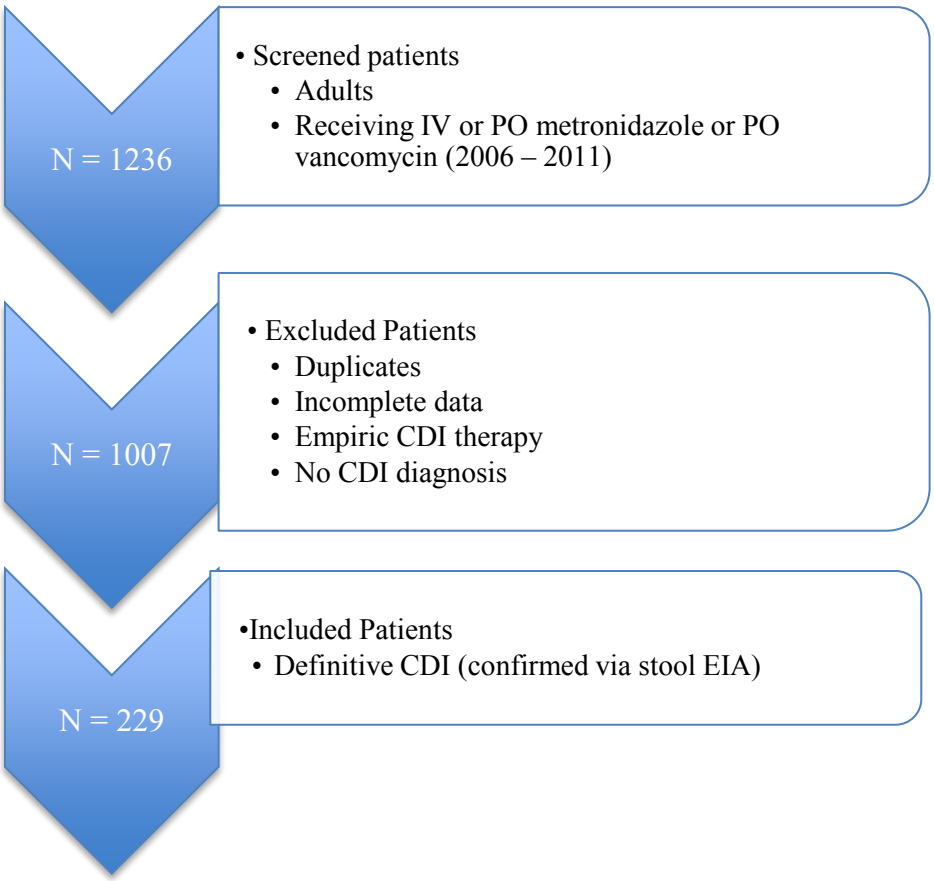


TABLE III
CDI CASE CHARACTERISTICS[a]

Characteristic	All (n=229)	Experienced Poor Outcome		
		No (n=159)	Yes (n=70)	P-value
Age, years	55 (18 – 94)	56 (18 – 94)	55 (22 – 86)	0.6617
Length of Stay (LOS), days	12 (1 – 192)	10 (1 – 95)	22 (3 – 192)	0.0002*
LOS post CDI diagnosis, days	6 (0 – 126)	4 (0 – 60)	12 (0 – 126)	0.0001*
Hospital-onset CDI	152 (66.4)	106 (66.7)	46 (66)	0.5020
Community-onset CDI	44 (19.2)	29 (18.2)	15 (21.4)	0.3410
Community-onset healthcare facility associated CDI	33 (14.4)	24 (15.1)	9(12.9)	0.4120
Clinical Presentations				
Diarrhea	189 (82.5)	129 (81.1)	60 (85.7)	0.2600
Abdominal pain	47 (20.5)	34 (72.3)	10 (21.3)	0.3840
Abdominal distension	38 (16.6)	28 (17.6)	10 (6.3)	0.3390
Colonoscopy or CT findings				
Pseudomembranous colitis	13 (5.7)	6 (3.8)	7 (10)	0.0630
Thickened colon	5 (2.2)	4 (2.5)	1 (1.4)	0.5370
Charlson comorbidity Index	4 (0 – 19)	4 (0 – 12)	4 (0 – 14)	0.4550
Presence of a comorbidity	205 (89.5)	140 (88.1)	65 (92.9)	0.1970
Concurrent infection	89 (42.6)	65 (40.9)	24 (34.3)	0.2140
COPD	11 (5.3)	9 (5.6)	2 (2.9)	0.2920
History of Cancer	46 (22)	29 (18.2)	17 (24.3)	0.1900
Type 2 diabetes mellitus	87 (41.6)	59 (37.1)	28 (40)	0.3930
HIV/AIDS	5 (2.4)	4 (2.5)	1 (1.4)	0.5160
History of Cardiovascular disease[b]	78 (37.3)	52 (33.7)	26 (37.1)	0.3060
Type 1 diabetes mellitus	10 (4.8)	5 (3.1)	5 (7.14)	0.1550
Inflammatory bowel disease (IBD)[c]	13 (6.2)	11 (6.9)	2 (2.9)	0.1830

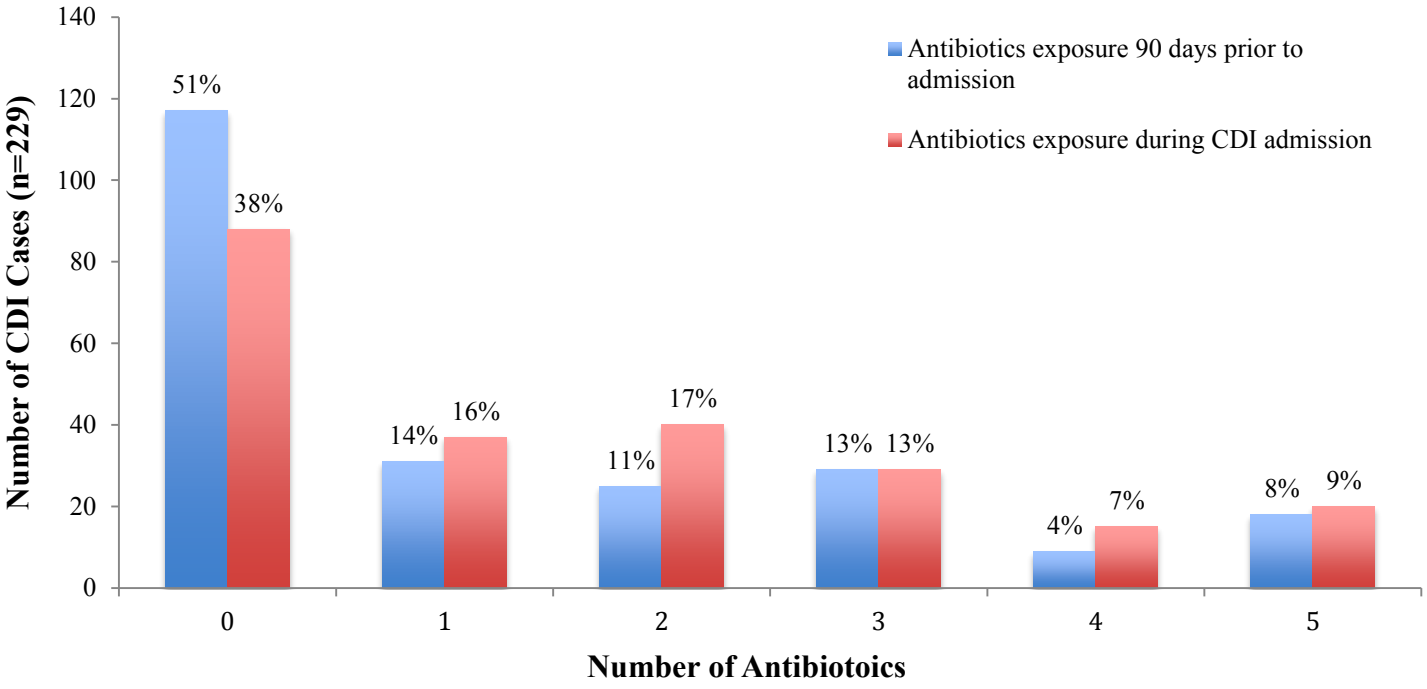
[a]Data reported as either median (range) or n (%).

[b]Cardiovascular disease was defined as the presence of heart failure, myocardial infraction, coronary artery disease, peripheral arterial or vascular disease [c] IBD was defined as the presence of ulcerative colitis and Crohn's disease diagnosis.

*Denotes significant difference (P<0.05).

Approximately 82% of the study population was exposed to at least one antibiotic 90 days prior to CDI diagnosis (TABLE IV). Overall, 62% and 49% of the CDI cases received an antibiotic concomitantly during CDI diagnosis admission and 90 days prior to admission, respectively. The majority of patients (80%) received at least one high-risk antibiotic prior to CDI diagnosis. Most patients were treated for <10 days. As seen from Figure 2, 25% and 29% of the study population were exposed to 3 or more antibiotics during CDI diagnosis admission and 90 days prior to admission, respectively.

Figure 2. Cumulative Antibiotic Exposure During and Prior to Admission



There was no significant difference in the number of CDI cases who were immunocompromised, receiving tube feeding or total parenteral nutrition, or in an ICU between the outcome groups (P>0.05, TABLE IV). However, there were significantly

more intubated patients who experienced poor outcome ($P<0.05$). Interestingly, all models constructed to assess outcome according to concordance identified intubation at the time of CDI diagnosis as a significant variable to control for (TABLE IV). The models constructed to analyze the difference in outcome between SCT and SDT according to SHEA/IDSA and ESCMID only identified being intubated at the time of CDI diagnosis as a significant variable. The model developed to assess outcome according to concordance to the Zar severity index identified intubation and ICU stay at the time of CDI diagnosis, as well as exposure to 4 antibiotics and residing at a nursing facility prior to admission, as significant variables.

TABLE IV
RISK FACTORS OF CDI[a]

Risk Factor	All (n=229)	Experienced Poor Outcome		
		No (n=159)	Yes (n=70)	P-value
Exposure to antibiotics during admission	141 (61.6)	97 (61)	44 (62.8)	0.4550
High-risk antibiotics	131 (57.2)	89 (55.9)	42 (60)	0.3370
Low-risk antibiotic	10 (4.4)	8 (5)	2 (2.9)	0.3630
<10 days	104 (45.4)	73 (45.9)	31 (44.3)	0.4670
10 – 20 days	18 (7.9)	12 (7.6)	6 (8.6)	0.4890
>20 days	19 (8.4)	12 (7.6)	7 (10.0)	0.3510
Exposure to antibiotics prior to admission	112 (48.9)	76 (47.8)	36 (51.4)	0.3580
High-risk antibiotics	109 (47.6)	74 (46.5)	35 (50)	0.3670
Low-risk antibiotic	3 (1.3)	2 (1.3)	1 (1.43)	0.6670
<10 days	75 (32.8)	52 (32.7)	23 (32.9)	0.5490
10 – 20 days	13 (5.7)	8 (5)	5 (7.1)	0.3610
>20 days	24 (10.5)	16 (10)	8 (11.4)	0.4600
Exposure to acid suppressant prior to diagnosis [b]	158 (69)	112 (70.4)	46 (65.7)	0.2870
< 10 days	73 (31.9)	54 (34)	19 (27.1)	0.1940
10-20 days	39 (17)	28 (17.6)	11 (15.7)	0.4430
> 20 days	46 (25.7)	30 (18.9)	16 (22.9)	0.3000
Exposure to opiates prior to diagnosis	132 (57.7)	87 (54.7)	45 (64.3)	0.1140
< 10 days	81 (35.4)	57 (35.8)	24 (34.3)	0.4710
> 10 days	51 (22.2)	30 (18.9)	21 (30)	0.0470*
Immunocompromised (IC)[c]	102 (39.4)	69 (43.4)	33 (47.1)	0.3510
At least 1 hospitalization in the past 6 months	164 (71.6)	113 (71.1)	51 (72.9)	0.4570
Received tube feeding during CDI diagnosis	26 (11.4)	17 (10.7)	9 (12.9)	0.3930
Intubated at CDI diagnosis	21 (9.2)	9 (5.7)	12 (17.1)	0.0070*
Received total parenteral nutrition during CDI diagnosis	7 (3.1)	4 (2.5)	3 (4.3)	0.3650
Residing at a nursing facility prior to admission	7 (3.1)	4 (2.5)	3 (4.3)	0.3650
Present in ICU during CDI diagnosis	105 (45.6)	74 (46.5)	31 (44.3)	0.4330

[a]Data reported as either median (range) or n (%)

[b]IC was defined if any of the criteria are met: patient receiving immune modulating, or antineoplastic, or 20mg prednisone equivalence for 14 days

[c]Acid suppressant was defined as the use of proton pump inhibitor or histamine receptor blocker.

*Denotes significant difference (P<0.05).

Baseline WBC count and SrCr as well as WBC count, temperature, albumin and SrCr at diagnosis were similar across all cases (TABLE V). There were 50 CDI cases that had missing albumin values (TABLE V). Of note, both ESCMID and Zar severity criteria incorporate albumin to differentiate between severe and non-severe illness (TABLE II). However, in scrutinizing these criteria, it is evident that albumin is not a necessary individual variable to differentiate severity of illness. For instance, following the Zar criteria, a CDI case that has ≥2 cumulative points would qualify as severe CDI regardless of presence or absence of an albumin value. However, if the CDI case fulfills only 1 of the Zar criteria other than albumin value, the severity of the case would be determined by albumin value. As such, in this study, CDI cases that were solely dependent on an albumin value to qualify as severe were dropped during the analysis. While the model created to assess concordance to ESCMID guideline was not affected, 16 CDI cases were dropped in the analysis for concordance to Zar severity criteria due to missing albumin values (n=213, TABLE VI).

TABLE V
LABORATORY VALUES, TREATMENT OPTIONS,
AND CONCORDANCE TO SEVERITY INDICES[a]

Risk Factors	All (n=229)	Experienced Outcome		
		No (n=159)	Yes (n=70)	P-value
Baseline WBC (1000 cells/mm^3)	9.5 (0 – 77.5)	8.8 (0.1 – 57.3)	10.3 (0 – 77.5)	0.0424*
WBC at CDI diagnosis (1000 cells/mm^3)	9.2 (0 – 77.2)	9 (0 – 66.9)	10.1 (0.3 – 77.2)	0.2771
Baseline SrCr (mg/dL)	1.2 (0.3 – 37.9)	1.3 (0.5 – 37.9)	1.2 (0.3 – 0.9)	0.2772
SrCr at CDI diagnosis (mg/dL)	1.1 (0.3 – 14.6)	1.1(0.3 – 14.6)	1.1 (0.4 – 8.1)	0.4446
Albumin at CDI diagnosis (mg/dL)‡	2.3 (0.1 – 4.6)	2.3 (0.9 – 4.6)	2.2 (0.1 – 4.4)	0.1524
Temperature at CDI diagnosis (^{0}C)	36.9 (33.6 – 39.9)	36.9 (35.6 – 39.1)	36.9 (33.6 – 39.9)	0.7628
Metronidazole monotherapy	156 (68)	–	–	–
Duration of metronidazole monotherapy, days	14 (2 – 55)	14 (4 – 42)	12 (2 – 55)	0.2145
Vancomycin monotherapy	23(10)	–	–	–
Duration of vancomycin monotherapy, days	14 (8 – 28)	14 (8 – 28)	12.5 (10 – 14)	0.3001
SHEA/IDSA concordant therapy	121 (53)	–	–	–
ESCMID concordant therapy	30 (13.1)	–	–	–
Zar concordant therapy‡‡	80 (37.6)	–	–	–
Poor outcome	70 (31)	–	–	–
recurrent CDI	6 (2.3)	–	–	–
treatment failure	31 (13.5)	–	–	–
30-day all-cause mortality	33 (14.4)	–	–	–

[a]Data reported as either median (range) or n (%)‡ n=179, as there were 50 missing values for albumin ‡‡ n=213

*Denotes significant difference (P<0.05).

TABLE VI
PROPORTIONS AND RISK OF EXPERIENCING POOR OUTCOME
AS STRATIFIED BY CONCORDANCE TO A SEVERITY INDEX[a]

Severity criteria	**Severity index-concordant therapy**	**Severity index-discordant therapy**	**Unadjusted Odds Ratio (95% CI), *P-value***	**Adjusted Odds Ratio (95% CI), *P-value***
SHEA/IDSA guideline (n= 229)	25/121 (20.6%)	45/108 (41.7%)	0.365 (95% CI: 0.2035 to 0.6532), 0.001*	0.437 (95% CI: 0.234 to 0.139), 0.009*
ESCMID guideline (n= 229)	6/30 (20%)	64/199 (32.2%)	0.527 (95% CI: 0.2054 to 1.3537), 0.183	0.511 (95% CI: 0.188 to 1.387), 0.189
Zar criteria (n= 213)	18/80 (22.5%)	47/133 (35.3%)	0.531 (95% C I: 0.2818 to 1.0013), 0.05	0.619 (95% CI: 0.317 to 1.211), 0.1620

[a]Data reported as proportion (%) of poor outcome per group.

*Denotes significant difference (P<0.05).

Due to the missing values of albumin, the models constructed to generate the output in TABLE V did not control for albumin. However, additional models were developed to assess the effect of albumin on risk of poor outcome and concordance to a severity index. After performing the regression for all the severity indices, the addition of albumin did not alter the main findings of TABLE VI (data not shown). Duration and type of antibiotics (high or low – risk) were also removed due to high collinearity.

B. Primary, Secondary, and Other Outcomes

Out of the 229 CDI cases, 31% experienced poor outcome (TABLE V). Combined, treatment failure and 30-day all-cause mortality were responsible for 91% of unfavorable outcomes. According to SHEA/IDSA, ESCMID, and Zar severity indices, 28%, 97%, and 55% of the cases experienced severe illness, respectively. Poor outcome occurred in 35%, 30%, and 28% of the severe CDI cases as defined by SHEA/IDSA, ESCMID, and Zar severity indices, respectively (TABLE II). Incidence of poor outcome was higher in CDI cases that did not receive SCT (TABLE VI).

After adjusting for variables, concordance to SHEA/IDSA severity index significantly reduced the odds of experiencing a poor outcome by 66% ($P<0.05$, TABLE VI). Albeit not significant, concordance to the ESCMID and Zar criteria also reduced the risk of experiencing a poor outcome. As seen in TABLE VII, Hosmer-Lemeshow test showed good fit for all the models ($P>0.05$). Also, in all severity indices, the SCT groups had fewer LOS post CDI diagnosis (TABLE VIII). Both unadjusted and adjusted for confounders, concordance to SHEA/IDSA and Zar indices significantly reduced LOS post diagnosis ($P<0.05$, TABLE VIII). Concordance to ESCMID resulted in a non-significant reduction. There was a non-significant increase in the LOS post diagnosis in

severe CDI cases according to SHEA/IDSA and Zar indices (<1 day, P>0.05, data not shown). This was not observed in the ESCMID group.

TABLE VII
MODEL PERFORMANCE AND DISCRIMINATION CURVE INFORMATION

	Model performance: Goodness-of-Fit	**Discrimination: Area Under the Curve**	
Indices	**Hosmer-Lemeshow χ^2 test (P-value)**	**Before cross-validation (95% CI)**	**After 10 cross-validation (95% CI)**
SHEA/IDSA guidelin	P=0.4208	0.720 (0.650 to 0.791)	0.568 (0.487 to 0.649)
ESCMID guideline	P=0.3875	0.717 (0.642 to 0.792)	0.593 (0.510 to 0.676)
Zar criteria	P=0.3868	0.718 (0.641 to 0.795)	0.550 (0.467 to 0.633)

TABLE VIII

EFFECT OF SEVERITY INDEX-CONCORDANCE THERAPY ON POST CDI DIAGNOSIS LENGTH OF STAY (LOS, DAYS)[a]

Severity criteria	**Severity index-concordant therapy**	**Severity index-discordant therapy**	**Unadjusted reduction in LOS post CDI diagnosis (95% CI), *P-value***	**Adjusted reduction in LOS post CDI diagnosis (95% CI), *P-value***
SHEA/IDSA guideline (n= 229)	4 (0 – 126)	10 (0 – 104)	-6 (95% CI: -8.056 to -3.944), 0.001*	-3.977 (95% CI: -5.243 to -2.712), 0.0001*
ESCMID guideline (n= 229)	5 (0 – 40)	6 (0 – 126)	-1 (95% CI: -3.976 to 1.976), 0.509	-0.500 (95% CI: -3.176 to 2.176), 0.713
Zar criteria (n= 213)	4 (0 – 126)	7 (0 – 104)	-3 (95% CI: -5.114 to -0.886), 0.006*	-3.994 (95% CI: -5.873 to -2.115), 0.0001*

[a]Data reported as median (range).

*Denotes significant difference (P<0.05).

The majority of CDI cases received PO metronidazole 500 mg every 8 hours as monotherapy (68%) for more than 10 days (88%). The remaining cases were treated with either PO vancomycin 125 mg every 6 hours as monotherapy (10%) or other therapies (22%). Other therapies included an alternative dose and/or route of metronidazole than recommended in the guidelines, combination therapy, and alternative treatments.

The incidence of poor outcome was 17% and 21% in the vancomycin and metronidazole monotherapy groups, respectively ($P>0.05$). After stratifying by severity of illness, there was no significant difference in the risk of poor outcome between monotherapy PO vancomycin 125 every 6 hours group and monotherapy PO metronidazole 500 mg every 8 hours ($P>0.05$, TABLE IX). TABLE X compares the risk of poor outcome between any metronidazole and vancomycin based therapies regardless of route and/or frequency and any possible combination therapy (receiving both metronidazole and vancomycin concurrently). Regardless of severity of infection and severity index, there was less risk of poor outcome in the metronidazole and vancomycin based therapy groups when compared to combination therapy. The models constructed to compare treatment modalities only included the aforementioned clinically pertinent variables.

TABLE IX
PROPORTIONS AND RISK OF POOR OUTCOME AS STRATIFIED BY SEVERITY OF ILLNESS[a] AND CDI MONOTHERAPY[b]

A. SHEA/IDSA guideline, proportion (%) of poor outcome (n=179)

Non-severe disease (n=134)			Severe disease (n=45)		
Metronidazole monotherapy	Vancomycin monotherapy	Adjusted OR (95% CI), *P-value*	Metronidazole monotherapy	Vancomycin monotherapy	Adjusted OR (95% CI), *P-value*
23/25 (92)	2/25 (8)	0.525 (95%: 0.111 to 2.494), 0.418	9/11 (82)	2/11 (18)	1.771 (95%: 0.215 to 14.567), 0.595

B. ESCMID guideline, proportion (%) of poor outcome (n=179)

Non-severe disease (n=7)			Severe disease (n=172)		
Metronidazole monotherapy	Vancomycin monotherapy	Adjusted OR (95% CI), *P-value*	Metronidazole monotherapy	Vancomycin monotherapy	Adjusted OR (95% CI), *P-value*
2/2 (100)	0 (0)	N/A	30/34 (88)	4/34 (12)	0.823 (95%: 0.256 to 2.650), 0.744

C. Zar criteria, proportion (%) of poor outcome (n=165)

Non-severe disease (n=73)			Severe disease (n=92)		
Metronidazole monotherapy	Vancomycin monotherapy	Adjusted OR (95% CI), *P-value*	Metronidazole monotherapy	Vancomycin monotherapy	Adjusted OR (95% CI), *P-value*
15/16 (94)	1/16 (6)	0.633 (95%: 0.0668 to 5.999), 0.690	14/17 (82)	3/17 (18)	1.124 (95%: 0.271 to 4.661), 0.872

[a]Severity of illness was defined according to the respective severity indices (TABLE II).

[b]Standard treatment was defined as oral metronidazole 500 mg Q8 hours and oral vancomycin 125 mg Q6 hours.

TABLE X
PROPORTIONS AND RISK OF POOR OUTCOME AS STRATIFIED BY SEVERITY OF ILLNESS[a] AND OTHER TREATMENT OPTIONS[b]

A. SHEA/IDSA guideline, proportion (%) of poor outcome (n=229)

Non-severe disease (n=166)			Severe disease (n=63)		
Combination therapy	**Metronidazole-based treatment**	**Adjusted OR (95% CI), *P-value***	**Combination therapy**	**Metronidazole-based treatment**	**Adjusted OR (95% CI), *P-value***
14/48 (29) [Ref. group]	23/48 (48)	0.066(95% CI:0.018 to 0.240), 0.001*	9/22 (41) [Ref. group]	11/22 (50)	0.079 (95% CI: 0.016 to 0.388), 0.002*
	Vancomycin-based treatment	**Adjusted OR (95% CI), *P-value***		**Vancomycin-based treatment**	**Adjusted OR (95% CI), *P-value***
	11/48 (23)	0.123 (95% CI: 0.030 to 0.522), 0.004*		2/22 (9)	0.074 (95% CI: 0.008 to 0.716), 0.025*

B. ESCMID guideline, proportion (%) of poor outcome (n=2290)

Non-severe disease (n=8)			Severe disease (n=221)		
Combination therapy	**Metronidazole-based treatment**	**Adjusted OR (95% CI), *P-value***	**Combination therapy**	**Metronidazole-based treatment**	**Adjusted OR (95% CI), *P-value***
1/3 (33) [Ref. group]	2/3 (67)	NA	22/67 (33) [Ref. group]	32/67 (48)	0.074 (95% CI: 0.028 to 0.193), 0.001*
	Vancomycin-based treatment	**Adjusted OR (95% CI), *P-value***		**Vancomycin-based treatment**	**Adjusted OR (95% CI), *P-value***
	0 (0)	NA		13/67 (19)	0.135 (95% CI: 0.044 to 0.416), 0.001*

TABLE X CONTINUED
PROPORTIONS AND RISK OF POOR OUTCOME AS STRATIFIED BY SEVERITY OF ILLNESS[a]
AND OTHER TREATMENT OPTIONS[b]

C. Zar criteria, proportion (%) of poor outcome (n=213)

Non-severe disease (n=96)			**Severe disease (n=117)**		
Combination therapy	**Metronidazole-based treatment**	**Adjusted OR (95% CI), *P-value***	**Combination therapy**	**Metronidazole-based treatment**	**Adjusted OR (95% CI), *P-value***
11/32 (34) [Ref. group]	15/32 (47)	0.096 (95 %CI: 0.026 to 0.353), 0.001*	10/33 (30) [Ref. group]	16/33 (49)	0.048 (95% CI: 0.009 to 0.242), 0.001*
	Vancomycin-based treatment	**Adjusted OR (95% CI), *P-value***		**Vancomycin-based treatment**	**Adjusted OR (95% CI), *P-value***
	6/32 (19)	0.243 (95% CI: 0.050 to 1.179), 0.079		7/33 (21)	0.075 (95% CI: 0.128 to 0.443), 0.004*

*Denotes significant difference (P<0.05)

‡Denotes significant difference (P<0.05)

[a] Severity of illness was defined according to the respective severity indices (Table 2)

[b]Other treatment options were defined as follows:
- Metronidazole-based treatment: metronidazole monotherapy regardless of dose or route
- Vancomycin-based treatment: vancomycin monotherapy regardless of dose or route. It also includes CDI cases that were initially treated with metronidazole, but then switched to vancomycin
- Combination therapy: vancomycin & metronidazole therapy started together or one therapy option added on to another

IV. DISCUSSION AND CONCLUSION

Antibiotic use is the primary risk factor for developing CDI [3]. With one in three antibiotics being used inappropriately [37], it is no surprise that CDI is associated with increasing incidence as well as high morbidity, mortality, and cost [1,18,38]. Clinical cure is contingent on differentiating between mild/moderate and severe CDI [9,15,16,20]. This classification has been shown to improve outcomes and is recommended by all major infectious disease treatment guidelines worldwide. However, the severity indices are inconsistent and even contradictory in their definitions of certain parameters and recommendations [9,15,16,20,22,39]. There is also limited data on the comparison of severity indices to predict best prognosis within the same patient population [17].

A. Primary Outcome

Given the significant clinical and economic impact of CDI, this study compared three major CDI severity indices in their ability to predict treatment outcome. The identification on of an index with the best prognostic value can assist clinicians to appropriately evaluate the severity of infection and select the optimal anti-CDI antibiotic.

In addition to the clinically and statically significant reduction in poor outcome concordance to SHEA/IDSA produced in this study population, the simplicity of SHEA/IDSA index may make it more clinically appealing and applicable as well. Conversely, ESCMID's extensive lists of possible criteria to qualify the majority of cases as severe profoundly limit its applicability. This is evident by 97% of the study population being classified as experiencing severe infection (TABLE IX). Moreover, from a clinical perspective, the likelihood of clinicians to consider every single criterion

(>15) listed under the ESCMID guideline is impractical.16 On the contrary, clinicians only need to remember 2 criteria (WBC count and SrCr) in order to practice evidence-based medicine according to the SHEA\IDSA guideline. Interestingly, concordance to the Zar criteria did not significantly reduce the risk of poor outcome, but significantly reduced LOS post CDI diagnosis.

The clinical significance of following SHEA/IDSA concordant therapy has also been documented [40,41]. Even at 38% adherence to SHEA/IDSAs' recommendations, Knaus et al. report that concordance to SHEA/IDSA non-significantly reduced 30-day hospital readmission, median cost after CDI diagnosis, and LOS [41]. Although these endpoints were not assessed in the current study, Knaus et al.'s study findings highlight the clinical and economical importance of adhering to guidelines. In another retrospective study, Brown and Seifert found concordance to SHEA/IDSA led to a near 40% reduction in complications as defined by death, infection recurrence, toxic megacolon, and surgery [40]. While Brown and Seifert's study was the first to associate the clinical benefits to severity index guided anti-CDI therapy, it was limited to the SHEA/IDSA severity index. The lack of data in comparing multiple guidelines and severity indices highlights the importance of the current study to identify the index that best predicts outcome. Moreover, it is encouraging that both studies had similar findings including the benefits of SCT as well as increased incidence of poor outcome in severe CDI cases. This is particularly noteworthy after considering that both studies assessed different time periods (2006 to 2011 versus April, 2011 to October, 2011) and populations (Illinois versus Texas).

The presence of more complications in severe CDI cases was also recorded in another

retrospective study [17]. Similar to this study, Gomez-Simmonds et al. investigated the difference in outcome between non-severe and severe CDI according to SHEA/IDSA, Zar, and hospital-specific severity indices. Their study supports the use of SHEA/IDSA and Zar indices to categorize severity of illness. However, unlike the current study, Gomez-Simmonds and colleagues only performed bivariate analysis to determine risk of poor outcome and did not adjust for potential confounders.

B. Secondary Outcome

Evidence and expert opinion surrounding metronidazole's ability to successfully treat non-severe CDI as efficiently as vancomycin is inconclusive. Although Zar et al. and other studies showed no difference in clinical outcome in non-severe CDI cases receiving metronidazole or vancomycin [15], other studies have found conflicting results [42].

Comparing vancomycin to metronidazole, vancomycin has many advantages over metronidazole including a lower minimum inhibitory concentration against *C. difficile,* narrower spectrum, higher fecal concentrations, minimal systematic absorption, and fewer side effects [9,16,43]. Despite these factors, recent CDI guidelines continue to advocate the use of metronidazole during non-severe and recurrent infections [9,15,20].

The cost difference between the two agents and the fear of PO vancomycin increasing the emergence of vancomycin-resistant enterococci (VRE) is believed to have persuaded clinicians to increasingly use the non-FDA approved metronidazole as the agent of choice against CDI [9]. Interestingly, the use of metronidazole has also been linked to emergence of VRE [16]. More importantly, the contribution of vancomycin to the incidence of VRE is not substantiated or established to be clinically relevant [16,44]. In terms of cost, the American Journal of Gastroenterology guideline against CDI estimates

a 10-day course of metronidazole and vancomycin to cost $22 and $100 – $680, respectively [20]. At UIHHSS, a 10-day course of oral metronidazole and vancomycin cost $299 and $388, respectively. These two factors and the lack of guidelines against CDI in the study period could have contributed to the disproportionate use of metronidazole in the current study. Similar to Brown and Seifert's article, the majority of discordant therapy occurred during the treatment of severe illness with metronidazole [40].

In this study, the vancomycin monotherapy group experienced fewer poor outcomes in comparison to metronidazole monotherapy (17% versus 21%, respectively). However, these were not statically significant. This is particularly interesting as this reduction in poor outcome was observed with a small sample size (n=23). It is possible the study was underpowered to detect an accurate estimate on the effect of vancomycin on clinical outcome. This finding is consistent with other findings [42,45]. In a recent meta-analysis that consisted more than 7000 patients, metronidazole group had higher treatment failure and recurrence rate than vancomycin group [45]. However, unlike other studies [15,23,42], the study did not find an advantage to using vancomycin monotherapy over metronidazole monotherapy in treating severe CDI.

Although there is a consensus on the timing of utilizing metronidazole and vancomycin monotherapy among the guidelines, there is no consensus on the criteria to clearly define severe-complicated CDI or its management via combination therapy [9,16,20]. While SHEA/IDSA recommend the use of PO vancomycin 500 mg every 6 hours and IV metronidazole 500 mg every 8 hours [10], ESCMID recommend surgical alternatives (colectomy) [11]. Alternatively, the American Journal of Gastroenterology

guideline recommends the use of oral and rectal vancomycin along with IV metronidazole [15]. These recommendations are largely based on expert opinion. The uncertainty of the benefits of combination therapy might explain SHEA/IDSA and American Journal of Gastroenterology guidelines against CDI to rate the strength of evidence for combination therapy as low [9,16]. However, combination therapy has been reported to improve clinical outcome in critically ill patients [46].

Due to the lack of clearly defined criteria and complicated nature of managing severe-complicated CDI, this study did not assess the incidence or outcomes of severe-complicated CDIs. Instead, the study assessed if there is any benefit of receiving combination therapy (receiving both metronidazole and vancomycin concurrently). As seen in TABLE X, metronidazole and vancomycin based treatment options had significantly fewer poor outcomes when compared to combination therapy. Although this might seem to contrast guideline recommendations, several studies have found no benefit to combination therapy [47,48]. Also, a recent meta-analysis did not find a difference in outcome between monotherapy and combination therapy [23]. In addition, a 2009 *in vitro* study showed no synergistic activity between metronidazole and vancomycin [49].

More importantly, if there were added benefits to combination therapy, classifying combination therapy as SDT would have theoretically biased the results towards favoring discordant therapy. However, the SDT group had higher incidences of poor outcome repeatedly (TABLE VI). Similarly, LOS post diagnosis was consistently higher in the SDT group (TABLE X). Thus, the study findings are rationale and plausible.

C. Other Outcomes

Concordance to a severity index reduced LOS and costs post-CDI diagnosis (TABLE VIII). At a given cost of $1,929 for room and board (at UIHHSS), concordance to SHEA/IDSA, ESCMID, and Zar may have reduced costs by up to $7,672, $965, and $7,704, respectively. Considering the reduction in poor outcomes in the SCT groups, it is no surprise that the LOS post diagnosis was also reduced. Similarly, a study in 2016 found concordance to SHEA/IDSA reduced LOS after diagnosis by 2 days and cost by $1,500 [41].

Of note, LOS post diagnosis was a continuous, non-normally distributed variable. Thus, logistic and linear regressions could not be implemented [36]. Although logarithmic and square root transformations were attempted to normally distribute the variable, it was to no avail. Transformation techniques are common in medical literature [46]. Thus, quantile regression model was constructed via backward elimination. Quantile regression quantifies the median effect of the independent variable on an outcome rather than the mean or average (linear regression) [50,51]. As such, quantile regression is less affected by outliers. Thus, this regression method can be implemented when dealing with an outcome that is non-normally distributed continuous variable.

Similar to the report in the American Journal of Gastroenterology guideline for CDI, 82% of this study's population was exposed to an antibiotic prior to developing CDI [20]. In addition to the selective pressure antibiotic causes, the disruption of gut microbiota affects the bile acid production and metabolism [52,53]. This is particularly important because the gut microbiota is responsible for bio-metabolizing primary bile acids to secondary. Although *C. difficile* spores are able to withstand the acidic environment in the colon, the germinated, vegetative bacteria are not able to survive in such harsh

environment [52]. However, in an antibiotic exposed individuals, the gut microbiome and the production of secondary bile acids is profoundly disrupted. This provides the suitable environment for *C. difficile* spores to germinate in the small intestine, colonize the colon, and cause the infection. Thus, antibiotic exposure has a direct and indirect effect in the development of CDI. This was illustrated in a murine model when Koenigsknecht and colleagues detected spore germination only 6 hours post antibiotic exposure (cefoperazone [0.5 mg/ml]) [53]. However, not all patients exposed to antibiotics develop CDI. Other factors including the pathogenicity of the *C. difficile* strain as well as patient's immune status, age, history of hospitalization, and comorbidities contribute to the development of CDI as well as recurrent CDI [16,33]. Conversely, not all patients with CDI had antibiotic exposure.

Patients without these traditional risk factors are referred to as experiencing community associated or community onset CDI [2,9,16]. While the cause of community acquired CDI has not been elucidated, its incidence has been reported to be increasing [2]. In a national survey conducted by the CDC, Lessa et al. estimate an incidence of 52 and 95 per 100,000 persons community and health care – associated CDI, respectively. Similarly, this study reported higher incidence of hospital onset CDI than community onset CDI (66% and 19%, respectively).

D. Limitation

The study has several limitations. The majority of the limitations are due to the study design: retrospective, single-center, and data collection time period. Due to the retrospective nature of the study, the presence or absence of diarrhea was recorded based only on clinicians' notes in the medial chart. The frequency of diarrhea episodes was not

available. Patient's use of medications including antibiotic exposure outside of the inpatient side of UIHHSS was also not available. Since the majority of the data were collected prior to the SHEA/IDSA and ESCMID guideline publication date, it is possible that many clinicians were not aware of vancomycin's potential clinical superiority over metronidazole especially in severe CDI cases. This, along with the increased cost of vancomycin and fear of VRE emergence, could have contributed to the majority of patients receiving metronidazole (66%). However, this also minimizes the likelihood of selection bias that is often associated with retrospective study.

Additionally, by virtue of the *a priori* definitions used [22], (9.6%) patients were recorded multiple times over the study period. Accounting for unique CDI cases only, the incidence of poor outcome still remained the same (31%). The incidence of severe illness in the unique CDI cases was 29%, 97%, and 65%, per SHEA/IDSA, ESCMID, and Zar severity indices, respectively. The median CCI, age, and LOS were 4 (range: 0 to 14), 56 (range: 18 to 94), and 13 (range: 1 to 130), respectively. These are all similar to the reported values earlier (TABLES III and V). Moreover, the risk of experiencing poor outcome between SCT and SDT remained similar to the output reported in TABLE VI. Regardless, this could have been a disastrous fault if the number of unique CDI cases was significantly lowered. Coincidentally, only less than 10% of the study sample was affected. Moreover, it is evident that eliminating the non-unique CDI cases did not affect the primary endpoint.

Another possible limitation is the use of an EIA kit to confirm CDI diagnosis. Although EIAs are infamous for their low sensitivity [9], UIHHSS's EIA kit, Meridian Premier™, has sensitivity value >90% [11–14]. Due to the lack of CDI guidelines and

high uptake of EIA kits during the study period, the use of the Meridian Premier™ EIA kit at UIHHSS was reasonable and, thus, unavoidable in this study. Moreover, it is well understood that specificities and sensitivities are usually inversely related [54]. At high specificity (>97%), it is not surprise Premier™'s has lower sensitivity. More importantly, the lower the sensitivity, the higher the likelihood stools were incorrectly labeled as negative EIA results (i.e. false negative). This may be the reason the majority (>50%) of CDI cases received empiric therapy and were excluded from this study. As such, the low sensitivity and high specificity most likely affected the number of cases being excluded rather than biasing the results. Thus, the use of the Meridian Premier™ is not expected to affect the outcome in this study.

As any retrospective single-center study, the generalizability of the study findings are limited to the study population [36]. The small sample size and lack of external validation also curtail the use of the findings in clinical settings. However, the study findings are similar to other studies conducted in more recent years [17,40,41]. More importantly, the results are clinically intuitive and rationally sound.

E. Conclusion

To the best of our knowledge, this is the first study to compare several severity indices as it relates to clinical end points. The findings suggest that concordance to SHEA/IDSA produced a clinically meaningful reduction in poor outcome as well as cost and LOS post CDI diagnosis. SHEA/IDSA's simplistic approach to stratify severity may also give it an edge over other indices. Conversely, the lack of significant reductions in outcome as well as classifying 97% of patients as severe case may suggest that

ESCMIDs' recommendations have limited clinical use. Streamlining ESCMID's severity criteria could potentially increase its clinical applicability and adaptability.

Although the vancomycin monotherapy group had fewer poor outcomes, there was no significant difference in the risk of experiencing poor outcome between metronidazole and vancomycin monotherapy groups regardless of severity. Conversely, the benefit of combination therapy remains unclear. Regardless, the sample sizes in these groups were small and inference from the results should be taken with caution.

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APPENDICES

APPENDIX A. STATA Output for Assessing the Risk of Experiencing Poor Outcome as Stratified by Concordance to a Severity Index: Multivariable Logistic Regression via Backward Selection

Risk of Experiencing Poor Outcome as Stratified by Concordance to SHEA/IDSA Criteria

Poor Outcome	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
Concordance to SHEA/IDSA	0.437	0.139	-2.590	0.009	0.234	0.817
Immunosuppressed$^{\phi}$	1.026	0.345	0.080	0.939	0.530	1.985
Age$^{\phi}$	0.992	0.012	-0.670	0.505	0.968	1.016
LOS pre CDI diagnosis$^{\phi}$	1.019	0.010	1.870	0.062	0.999	1.040
Charlson Comorbidity Index$^{\phi}$	1.109	0.083	1.390	0.164	0.958	1.284
Exposed to 4 antibiotics prior to admission	4.219	3.076	1.970	0.048	1.011	17.611
Intubated at CDI diagnosis	3.451	1.689	2.530	0.011	1.322	9.008
Baseline WBC	1.042	0.021	2.040	0.041	1.002	1.084
_cons	0.266	0.189	-1.870	0.062	0.066	1.068

Risk of Experiencing Poor Outcome as Stratified by Concordance to ESCMID Criteria

Poor Outcome	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
Concordance to ESCMID	0.511	0.260	-1.320	0.187	0.188	1.387
Immunosuppressed$^{\phi}$	1.133	0.364	0.390	0.697	0.604	2.125
LOS pre CDI diagnosis$^{\phi}$	1.020	0.010	1.950	0.051	1.000	1.040
Charlson Comorbidity Index$^{\phi}$	1.073	0.065	1.170	0.243	0.953	1.207
Baseline WBC	1.054	0.021	2.610	0.009	1.013	1.096
Intubated at CDI diagnosis	3.725	1.801	2.720	0.007	1.444	9.611
Exposed to 4 antibiotics prior to admission	5.371	3.909	2.310	0.021	1.290	22.366
_cons	0.118	0.055	-4.500	0.000	0.047	0.295

Risk of Experiencing Poor Outcome as Stratified by Concordance to Zar Criteria

Poor Outcome	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
Concordance to Zar	0.619	0.212	-1.400	0.162	0.317	1.212
Immunosuppressed$^{\phi}$	1.162	0.386	0.450	0.651	0.606	2.227
LOS pre CDI diagnosis$^{\phi}$	1.018	0.010	1.720	0.085	0.998	1.039
Charlson Comorbidity Index$^{\phi}$	1.059	0.066	0.910	0.361	0.937	1.196
Baseline WBC	1.050	0.021	2.410	0.016	1.009	1.092
Intubated at CDI diagnosis	3.723	1.867	2.620	0.009	1.393	9.950
Exposed to 4 antibiotics prior to admission	4.757	3.420	2.170	0.030	1.162	19.470
_cons	0.144	0.070	-3.970	0.000	0.055	0.374

$^{\phi}$ Represents the variables that were forced in.

APPENDIX B. STATA Output for Assessing Effect of Severity Index-Concordance therapy on Post CDI diagnosis Length of Stay: Multivariable Quantile Regression via Backward Selection

Effect of SHEA/IDSA-Concordance therapy on Post CDI diagnosis Length of Stay

LOS Post CDI Diagnosis	Coef.	Std. Err.	t	P>t	[95% Conf.	Interval]
Concordance to SHEA/IDSA	-3.977	0.642	-6.190	0.000	-5.243	-2.712
Immunosuppressed$^{\phi}$	-0.597	0.671	-0.890	0.375	-1.919	0.726
Age$^{\phi}$	-0.023	0.025	-0.910	0.365	-0.072	0.027
Charlson Comorbidity Index$^{\phi}$	-0.159	0.149	-1.070	0.286	-0.452	0.134
Absence of signs and symptoms at CDI diagnosis	2.528	0.978	2.590	0.010	0.601	4.456
Pseudomembranous colitis	2.170	1.344	1.610	0.108	-0.480	4.821
Exposed to 5 antibiotics during admission	6.653	1.169	5.690	0.000	4.349	8.957
Acid suppressant use >20 days prior to diagnosis	2.432	0.904	2.690	0.008	0.649	4.214
Exposed to 3 antibiotics prior to admission	-2.568	0.957	-2.680	0.008	-4.455	-0.682
Acid suppressant use <10 days prior to diagnosis	-0.483	0.696	-0.690	0.488	-1.854	0.888
Residing at a nursing facility prior to admission	-8.023	1.680	-4.770	0.000	-11.335	-4.710
Present in ICU during CDI diagnosis	1.665	0.660	2.520	0.012	0.364	2.966
Received total parenteral nutrition during CDI diagnosis	16.830	1.822	9.230	0.000	13.237	20.422
Receiving tube feeding at CDI diagnosis	5.063	0.983	5.150	0.000	3.125	7.000
Intubated at CDI diagnosis	-5.426	1.143	-4.750	0.000	-7.678	-3.174
At least 1 hospitalization in the past 6 months	-1.875	0.733	-2.560	0.011	-3.320	-0.430
_cons	10.267	1.478	6.950	0.000	7.354	13.181

Effect of ESCMID-Concordance therapy on Post CDI diagnosis Length of Stay

LOS Post CDI Diagnosis	Coef.	Std. Err.	t	P>t	[95% Conf.	Interval]
Concordance to ESCMID	-0.500	1.358	-0.370	0.713	-3.176	2.176
Immunosuppressed$^{\phi}$	0.000	0.972	0.000	1.000	-1.915	1.915
Charlson Comorbidity Index$^{\phi}$	-0.500	0.188	-2.670	0.008	-0.870	-0.130
Received total parenteral nutrition during CDI diagnosis	16.500	2.666	6.190	0.000	11.247	21.753
Exposed to 5 antibiotics during admission	5.000	1.646	3.040	0.003	1.756	8.244
Receiving tube feeding at CDI diagnosis	4.500	1.510	2.980	0.003	1.525	7.475
_cons	7.000	1.059	6.610	0.000	4.912	9.088

Effect of Zar-Concordance therapy on Post CDI diagnosis Length of Stay

LOS Post CDI Diagnosis	Coef.	Std. Err.	t	P>t	[95% Conf.	Interval]
Concordance to Zar	-3.994	0.953	-4.190	0.000	-5.873	-2.115
Immunosuppressed$^{\phi}$	-1.399	0.953	-1.470	0.144	-3.278	0.480

Charlson Comorbidity Index[ϕ]	-0.260	0.187	-1.380	0.168	-0.629	0.110
Received total parenteral nutrition during CDI diagnosis	14.256	2.410	5.920	0.000	9.505	19.008
Exposed to 5 antibiotics during admission	9.536	1.565	6.100	0.000	6.451	12.621
Exposed to 2 antibiotics during admission	-2.582	1.156	-2.230	0.027	-4.861	-0.304
Colon Thickening	-4.888	2.339	-2.090	0.038	-9.500	-0.277
Baseline SrCr	0.614	0.072	8.570	0.000	0.472	0.755
SrCr at CDI diagnosis	-0.775	0.240	-3.230	0.001	-1.248	-0.302
_cons	9.461	1.154	8.200	0.000	7.185	11.736

[ϕ] Represents the variables that were forced in.

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PUBLICATIONS

Moraski GC, Seeger N, Miller PA, Oliver AG, Boshoff HI, Cho S, **Mulugeta S** et al. Arrival of Imidazo[2,1-b]thiazole-3-carboxamides: Potent Anti-tuberculosis Agents that Target QcrB. [Submitted on Dec. 18, 2015 to American Chemical Society Infectious Disease]

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POSTER AND ORAL PRESENTATIONS

Mulugeta S, Wenzler E, Soriano M, Zar F, Danziger L. Differences in *Clostridium difficile* infection outcomes between guideline concordant and discordant therapy
- Poster Presentation: ICHP Spring Meeting, East Peoria, IL – April, 2016

Mulugeta S, Wenzler E, Soriano M, Zar F, Danziger L. Differences in *Clostridium difficile* infection outcomes between guideline concordant and discordant therapy
- Poster Presentation: UIC-COP Research Day, Chicago, IL – February, 2016

Mulugeta S, Wenzler E, Soriano M, Zar F, Danziger L. Differences in *Clostridium difficile* infection outcomes between guideline concordant and discordant therapy
- Poster Presentation: ASHP Annual Conference, New Orleans, LA – December, 2015

Mulugeta S, Soriano M, Zar F, Walton S, Danziger L. Predicting Severe *Clostridium difficile* Infection
- Poster Presentation: IPhA Annual Conference, Lombard, IL – September, 2015

Grzelak E, Choules M, Hwang C, Nam J, Yu Y, Cai G, Gao W, Lankin D, McAlpine J, **Mulugeta S**, et al. (HP)TLC-bioautography-ms/nmr – a new tool for the search of anti-tuberculosis lead compounds
- Poster presentation: The American Society of Pharmacognosy Meeting, Copper Mountain, CO – July, 2015

Mulugeta S, Soriano M, Zar F, Walton S, Danziger L. Predicting Severe *Clostridium difficile* Infection
- Poster Presentation: UIC-COP Research Day, Chicago, IL – February, 2015

Mulugeta S. Identifying and Validating Markers to Predict Severity of *Clostridium Difficile*-Associated Diarrhea
- Oral Presentation: Riback Committee, Chicago, IL – June, 2014

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