



# A Real-World Assessment of Clinical Outcomes and Safety of Eravacycline: A Novel Fluorocycline

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## ABSTRACT

**Background:** Eravacycline is a novel fluorocycline approved for treatment of intraabdominal infections, with a broad spectrum of activity against a range of pathogens including multidrug-resistant species, including ESBL- or KPC-producing isolates. It is approved for twice-daily dosing with no need for adjustment in renal dysfunction. In the concomitant administration with CYP 3A4-inducing drugs, eravacycline dosing should be modified.

**Objective:** To evaluate the efficacy and safety of eravacycline in a range of infections such as intraabdominal infections, pneumonia and diabetic foot infections in seriously ill patients.

**Methods:** A retrospective observational cohort study using electronic patient records of 50 consecutive patients administered eravacycline during inpatient acute care admission or as part of outpatient antibiotic therapy (OPAT).

**Results:** Therapy of 1.5 mg/kg q24h was initiated in the hospital in most patients, although some of the less sick were managed in the office or OPAT setting. All patients concluded their management outside of the hospital. Of the 50 patients, 47 (94%) achieved clinical resolution of their infection and 3 (6%) clinical failures occurred. Only three (6%) patients did not have comorbidities, three had a single comorbidity (6%), and the majority (88%) of patients had two or more comorbidities. Most common infections were intraabdominal (36%), pneumonia (18%), diabetic foot (12%), spontaneous bacterial peritonitis (8%) and empyema (8%). Almost half of infections had more than one pathogen isolated, and resistant isolates were frequent. The drug was well tolerated with only two reports of nausea, which did not result in treatment discontinuation, and in 30 days of post-eravacycline therapy only one case of *Clostridioides difficile*.

**Conclusions:** In this real-world setting, eravacycline demonstrated a similar high level of clinical efficacy as seen in clinical trials, 94%, in a variety of infections, including against multidrug-resistant bacteria, and was well tolerated.

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### Key Summary Points

Complex patients with multiple comorbidities, concomitant medications, different social or demographic groups and older individuals are often not included in clinical trials; real-world studies and data can demonstrate the safety and efficacy of an antibiotic in real clinical settings.

Eravacycline can be administered in single daily dosing, allowing for use in both inpatient and outpatient settings. A cohort of 50 patients received eravacycline for a variety of infections during inpatient acute care admission or as part of outpatient antibiotic therapy (OPAT).

Forty-seven of the 50 patients achieved clinical resolution; eravacycline was well tolerated with nausea the only adverse event reported and no patient discontinued treatment. Single daily dosing enabled all patients to receive their final dose of eravacycline in an outpatient location or at home.

*Clostridioides difficile* infection (CDI) is a common and problematic aftereffect of empirical broad-spectrum antibiotic therapy. Importantly, only one patient treated with eravacycline developed CDI at 30 days post-treatment even though a large proportion of patients had reported a CDI in the 12 and 6 months prior to treatment.

Eravacycline showed levels of clinical success and microbiologic outcomes that are in line with the efficacy of eravacycline in clinical trials, including among infections with ESBL- or KPC-producing isolates, and in a challenging group of patients with few side effects.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.12999617>.

## INTRODUCTION

Globally, the constantly increasing prevalence of multidrug-resistant (MDR) pathogens continues to pose significant issues in the contemporary healthcare systems [1]. MDR pathogens include both gram-positive and -negative species; these include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), and Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae*. In addition, the carbapenem-resistant non-fermenters, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, are regarded as priority target pathogens [2]. These challenging organisms are found in a wide range of infections such as pneumonia, urinary tract, intraabdominal and skin infections. Thus, it is essential that antibiotics that are active against these resistant phenotypes be available to clinicians.

Additionally, patients with underlying comorbid conditions are at increased risk for recurrent infections as well as developing CDI, which is a leading cause of healthcare-associated infection; *C. difficile* infection (CDI) is associated with high morbidity, mortality and economic costs [3, 4]. CDI is also a common occurrence following empirical broad-spectrum antibiotic treatment for other infections, presenting a clinical conundrum in the selection of antibiotics with lower risk of CDI development, but remains effective against resistant isolates (phenotypes?).

Eravacycline, a novel fully synthetic fluorocycline, exerts its antibacterial activity by reversibly binding to the ribosomal 30S subunit [5]. It has been shown in vitro that eravacycline has a tenfold higher affinity for ribosomal binding than tetracycline and inhibited protein translation at fourfold lower concentrations than the class progenitor drug, tetracycline.

Notably, eravacycline is bactericidal against some strains of *A. baumannii*, *E. coli* and *K. pneumoniae* [5–7].

Eravacycline has been shown to have antibacterial activity against a wide range of gram-positive and -negative aerobes and anaerobic species. Eravacycline has been demonstrated to be active against pathogens found in intraabdominal infections for which it is approved in the US [8–10] and Europe [11]. Minimum inhibitory concentrations (MIC) 90 s of these species include *E. coli*, including MDR strains (0.25–0.5 ug/ml), *Citrobacter freundii* (1–2 ug/ml), *K. pneumoniae* (1–2 ug/ml), *Klebsiella oxytoca* (0.5–1.0 ug/ml), MRSA (0.06–0.12 ug/ml), *Enterococcus faecalis*, both vancomycin susceptible and vancomycin resistant (0.12 ug/ml), and *Streptococcus* species (0.03–0.12 ug/ml) including the *Streptococcus anginosus* and *S. mitis* groups. Anaerobic pathogens include *Bacteroides fragilis* (1.0 ug/ml), *B. caccae* (0.5 ug/ml) and other members of this sub-group. It is also active against *Clostridium perfringens* (1.0 ug/ml) and *Clostridiodes difficile* including vancomycin-resistant strains (0.016–0.06 ug/ml) [12]. Among the non-fermenters, eravacycline is not active against *P. aeruginosa*, but does exhibit good activity against *A. baumannii* including carbapenem-resistant strains (2.0 µg/ml) [13].

Eravacycline does not appear to demonstrate antagonism toward other commonly used agents, most notably those isolated in the clinical trials.

Intravenous (IV) eravacycline demonstrates virtual dose-proportional pharmacokinetics over the range 0.3–3.0 mg/kg. AUC/MIC is the best predictor of efficacy. Multiple dosing of eravacycline at 1 mg/kg given over 12 h for 60 min yielded a C max value of 2125 ng/ml at day 1 and 1825 ng/ml at day 10 providing an AUC from time 0 to 12 h of 405 and 6309 ng/h/ml. Newman et al. [14] evaluated four different dosing regimens, specifically 1.5 mg/kg q24 over 30 min or 60 min. These two dosing regimens provided AUC<sub>0–24</sub> of 6003 ng/ml and 7171 ng/ml, respectively, at day 1. The data at day 10 showed 8051 ng/h/ml and 7592 ng/h/ml, respectively. The terminal half-life of eravacycline ranged from approximately 11 h on day 1 to approximately 30 h on day 10, thus

substantiating the once-daily dosing, which is essential when used in the outpatient setting.

Age, gender and race had no clinically relevant effects on the pharmacokinetics of eravacycline [14]. Eravacycline dosing should be reduced by 50% when given concomitantly with CYP3A4 inducers such as rifampin or phenytoin [15]. Renal failure has no clinical relevance for eravacycline dosing including in patients with end-stage renal disease (ESRD) [16]. Elevations in plasma concentrations are observed with all classes of hepatic failure. The efficacy of eravacycline has been demonstrated in intraabdominal infections in two randomized phase 3 clinical trials, IGNITE1 [17] and IGNITE4 [18]. However, as stated earlier, these data, although useful, do not indicate the potential clinical value in a real-world setting. We undertook an evaluation of the efficacy and safety of 50 patients with a range of infections treated with eravacycline in both hospital and office settings.

## METHODS

The study was a retrospective observational cohort of 50 consecutive patients prescribed eravacycline during an inpatient acute care admission or as part of outpatient antibiotic therapy (OPAT). All patients were managed throughout their care by a Metro Infectious Disease Consultant (MIDC) provider. Once discharged from the facility, all characteristics were collected from the electronic patient records. The study was approved by the Western Institutional Review Board (reference no. 20192083) and was performed in accordance with the Declaration of Helsinki.

All patients were identified via the routine institutional identification process of starting and reviewing drugs, including all relevant medical information, all hospitalization records as well as ID clinician notes and charts as appropriate. All information was collected in the usual manner by home infusion clinicians, but final analysis and tracking of patients through the case records were performed by the primary investigator (PI), with subsequent

review and validation of information by the co-PI.

Baseline characteristics collected included gender, age, weight, ethnicity, concomitant therapy immediately (30 days) prior to eravacycline, culture results, diagnosis or infection source, daily dose, location of first dose, location of last dose, renal function (CrCl), comorbidities, *C. difficile* history (in last 12 months), prior hospitalization within 90 days and history of gram-negative or -positive multidrug resistance (infection or documented colonization).

All patients were dosed on a once-daily regimen based on 1.5 mg/kg given over 60 min once a day for a period at the clinician's discretion.

## Outcomes

The primary outcome was assessment of the clinical outcomes and safety of eravacycline as assessed by the treating physician. Clinical outcomes were recorded as successful or unsuccessful and were defined by resolution or persistence of clinical symptoms. Safety was assessed by evaluation of all reported adverse events (AEs), regardless of the relationship to the study drug.

Secondary outcomes included:

1. Incidence of *C. difficile* infection (CDI) [measured by symptom assessment and subsequent Xpert (Cepheid)] at 2 weeks and 30 days post-completion of eravacycline;
2. Sub-analysis of the primary outcome according to:
3. All-cause readmission rates;
4. Infection-related readmission;
5. All-cause mortality rates;
6. Proportion of patients who received antibiotics post-discontinuation of the "study" treatment course that developed CDI;
7. Proportion of patients who did not receive antibiotics post-discontinuation of the "study" treatment course that developed CDI;
8. Adverse drug events during treatment (regardless of relationship to study drug);

9. Discontinuation of eravacycline based on the need for further antibiotics or an adverse event.

## Population and Sample Selection

Inclusion criteria: any patient admitted to the hospital or started as an outpatient that had received eravacycline.

Exclusion criteria:

1. Patients treated with a broad-spectrum antibiotic such as piperacillin/tazobactam, meropenem or ertapenem for > 72 h before transition to eravacycline.
2. Patients who were admitted with CDI or developed CDI within the first 96 h.

Patients were identified through provider referral to the study and were assessed for inclusion/exclusion criteria by the principal investigator and through electronic medical record documentation. All data collected on these patients were unidentified and did not include identifiable patient health information. Data collection was limited to the baseline characteristics and general object information.

All patient identifiers recorded were stored on Metro Infectious Disease Consultant computers on a secure network in a password-encrypted folder. Baseline characteristics such as past medical history were collected. Additionally, for the purposes of correcting for compounding variables, gender and race were also collected. All non-identifiable data collected and organized in aggregate form may be used for presentation and/or publication purposes.

## Statistics

Statistical analysis was conducted with de-identified data, and aggregate reported results maintained continued to be deidentified. Primary outcomes will be analyzed using descriptive and frequency statistics to allow for observation and comparison of outcomes between both disease and patient subsets. Statistical analysis will be conducted for the following secondary outcomes: incidence of CDI

at 2 weeks, 30 days and 90 days post-treatment, treatment outcome, readmission rates, requirement of subsequent antibiotics for the same infection and adverse drug events during treatment.

## RESULTS

Fifty consecutive patients met the study criteria. Baseline demographics are shown in Table 1. Mean age was 56.1 years with a range of 19–94 years; median age was 60.60, with an IQR of 18.75. The cohort was split male to female 25:25. The majority of patients were Caucasian with a mean weight of 80 kg. The majority (88%) of patients had two or more comorbidities, while three (6%) patients reported no comorbidities. More than half of patients had either hypertension or diabetes mellitus, but 16 (32%) patients had both hypertension and diabetes. The mean Charlson Comorbidity Index was 3.3 (median 3) with a range of 0–6 (IQR 2) (Table 1).

Thirty-eight patients were initially treated in the hospital, and 12 (24%) were started on eravacycline in a clinical office setting. All patients received their last treatment dose outside the hospital setting: 39 (79%) patients in a clinical office, 6 (12%) at home, 2 (4%) in a long-term acute care specialty hospital, and 1 (2%) each in long-term acute care (LTAC), skilled nursing facility (SNF) and home care that were taught how to infuse in the office (Table 2).

The most frequent infection sources were abdominal 17 (34%); there were 5 abscesses, bowel perforation (2), pelvic wound (3), pelvic ulceration (2), endocarditis (1), cholecystitis with IP drain (1), peritonitis (1) and infection secondary to surgery (1). Pneumonia was the next most common infection type with nine (18%) patients, and six patients (12%) had diabetic foot infections; spontaneous bacterial peritonitis (SBP) and empyema were reported in four (8%) patients each (Table 3).

Forty-eight of 50 received 1.5 mg/kg q24 over 60 min while 2 remaining patients reporting nausea received eravacycline 1.5 mg/kg q24 over 90 min.

Forty-eight patients were culture positive, and two patients were culture negative (Table 1). The most frequent pathogens isolated were MRSA 22, *E coli* 17 and VRE 14 with ESBL producing GNB 7 and KPC Enterobacteriaceae 5. *Acinetobacter* species were cultured in seven patients. Twenty-five infections were a single species with 24 having 2 or more pathogens (Table 4).

CDI was observed in 20 of 50 patients in the prior 12 months, 13 of these in 6 months and 7 in the prior month to eravacycline therapy (Table 1) with only 1 (2%) case of CDI reported within 30 days post-eravacycline treatment (Table 5). This patient had a history of five recurrences of CDI with management with bezlotoxumab and multiple fecal microbiome transplants. One patient reported CDI at 90 days; however, at 2 months post eravacycline, they were treated with augmentin for a sinus infection.

### Clinical Outcomes

Clinical resolution was reported in 47 of 50 patients (94%), 3 clinical failures occurred, two patients required further antibiotics, and one had a hospital readmission related to infection (Table 5). None of the clinical failures reported *C. difficile* post-eravacycline treatment. Of the three patients who reported clinical failure, all had resistant pathogens cultured; one patient had ESLD and PVD, was HIV positive and bacteremic, required subsequent antibiotic therapy and was readmitted to hospital related to infection. The second had a history of recurrent UTIs plus an indwelling catheter as well as COPD, HTN and HLD and required further antibiotics; the third case had uncontrolled diabetes with poor circulation, which contributed to the diabetic foot infection but did not require further antibiotics (Table 6). All-cause re-admission occurred in two cases, and two reports of nausea were recorded as adverse events, but there were no discontinuations of eravacycline. No mortality reported. Table 5 shows clinical and safety outcomes. The one patient who reported CDI 30 days post-eravacycline treatment did achieve clinical resolution

**Table 1** Baseline demographics of 50 patients treated with eravacycline

	<i>N</i> = 50 <i>n</i> (%)
Age (years)	
Mean	56.1
Range	19–94
Gender	
Male	25 (50)
Female	25 (50)
Race	
Caucasian	34 (68)
African American	12 (24)
Hispanic	3 (6)
Asian	1 (2)
Weight (kg)	
Mean	80
Range	45–114
Comorbidities	
Hypertension <sup>a</sup>	29 (58)
Diabetes mellitus <sup>a</sup>	27 (54)
HLD	12 (24)
COPD	11 (22)
PVD	9 (18)
ESRD	4 (8)
ESLD	4 (8)
Cancer	3 (6)
HIV	2 (4)
No comorbidities	3 (6)
Charlson Comorbidity Index (CCI)	
Mean	3.3
Range	0–6
Prior history	
Antibiotics in past 7 days	4 (8)
Antibiotics in past 30 days	18 (36)

**Table 1** continued

	<i>N</i> = 50 <i>n</i> (%)
Hospitalization in prior 3 months	16 (32)
History of MDR GNB infection	13 (26)
Prior CDI	
Past 12 months	20 (80)
Past 6 months	13 (26)
Past 1 month	7 (14)

*HLD* hyperlipidemia, *COPD* chronic obstructive pulmonary disease, *PVD* peripheral vascular disease, *ESRD* end-stage renal disease, *ESLD* end-stage liver disease, *MDR* multidrug resistance, *GNB* gram-negative bacteria, *CDI* *Clostridium difficile* infections

<sup>a</sup> Sixteen patients had both diabetes and hypertension

**Table 2** Administration location of eravacycline

Location	First dose <i>N</i> = 50 (%)	Last dose <i>N</i> = 50 (%)
Office	12 (24)	39 (78)
Hospital	38 (76)	0
Home health	0	6 (12)
LTSCF	0	2 (4)
Trained HC	0	1 (2)
LTAC	0	1 (2)
SNF	0	1 (2)

*LTSCF* long-term specialty care facility, *HC* home care, *LTAC* long-term acute care, *SNF* skilled nursing facility

of their initial infection (bowel perforation, group B *Streptococcus*); this patient had ESRD and ESLD and had been hospitalized in the 90 days prior to treatment, but had no history of *C. difficile* in the year prior to the study.

## DISCUSSION

This descriptive real-world evaluation of eravacycline was undertaken to determine the

**Table 3** Infection source by clinical outcomes

Infection type	Total <i>N</i> = 50 <i>N</i> (%)	Clinical resolution ( <i>N</i> = 47) <i>n</i> (%)	Duration of treatment (days)	Clinical failure ( <i>N</i> = 3) <i>n</i> (%)
Intraabdominal	17 (34)	16 (34)	18 (mean), 14 (median)	1 (33.3)
Pneumonia	9 (18)	9 (19)	9 (mean, median)	0
Diabetic foot	6 (12)	6 (12.7)	17 (mean), 14 (median)	0
SBP	4 (8)	4 (8.5)	5.5 (mean), 6 (median)	0
Empyema	4 (8)	3 (6.3)	18.6 (mean), 14 (median)	1 (33.3)
Skin	6 (12)	5 (10.6)	16 (mean), 14 (median)	1 (33.3)
UTI	2 (4)	2 (4.2)	5 (mean, median)	0
Bacteremia	2 (4)	2 (4.2)	26 (mean, median)	0

*SBP* spontaneous bacterial peritonitis, *UTI* urinary tract infection

efficacy and safety in a range of infection types. Eravacycline is approved in the US and Europe for intraabdominal infections based on one phase 2 study, which enabled two randomized, double-blind, double-dummy, multinational, non-inferiority phase 3 studies comparing eravacycline to meropenem in IGNITE1 and ertapenem in IGNITE4 to be conducted. The clinically evaluable populations showed efficacy of 92.9% and 96.9% in the two trials, respectively, compared with 94.5% and 96.1% for ertapenem and meropenem, respectively. Lan et al. [19] conducted a systematic review and meta-analysis of eravacycline in IAI and concluded that the clinical efficacy of eravacycline is as high as that of the comparator drugs and is as well tolerated. This study cohort of patients could be generally regarded as quite sick based on the mean CCI of 3.3 with some patients having a CCI of 6.

There have been three previously reported real-world clinical experience studies involving eravacycline [20–23], the largest of which reported on 35 patients. These studies include hospital and OPAT settings. The majority of patients across all three studies were males, mid-50s in age, with a mean Charlson Comorbidity Index (CCI) of 3, and a large proportion had comorbidities, including diabetes and moderate or severe kidney disease. In two studies, 68.4% [21] and 89% [23] of patients had  $\geq 1$  risk

factors for multidrug-resistant organisms based on recent hospitalization and antibiotic exposure.

Intraabdominal infections comprised 50% > of infections in two studies [20–22] and 34% in the third [23]; the other predominant infections were respiratory tract infections, bone and joint, bacteremia, and skin and soft tissue infections. All patients in the study by Alosaimy et al. [23] were admitted to the ICU at some stage, demonstrating the complex nature of this patient cohort. The most frequently cultured pathogens from all studies included *K. pneumoniae*, 4 of which were with CRE, *E. coli*, *Enterobacter cloacae*, *A. baumannii*, *E. faecium*, MRSA, *Enterococcus* sp. and VRE. Of note, in the Alosaimy et al. study [23], four patients had polymicrobial infections, and CRE was present in all studies.

In the study by Lusted [20], 62.5% of patients had clinical success. Hwang et al. [21, 22] reported the clinical cure in 63.2% and 5% with improvement. Alosaimy et al. [23] reported 70% clinical success because of persistent signs and symptoms of infection, 22% were considered clinical failure, and, reflective of the critical and complex patient cohort, 12.5% experienced recurrence and 7.5% died. Notably, seven of eight (88%) patients with CRE infections survived, and 91% of patients did not have 30-day recurrence. The authors [23] noted that

**Table 4** Baseline microbiology, culture and pathogen of 50 patients

	<i>N</i> = 50 (%)
No culture	2
Culture positive	48
Number of pathogens per infection	<i>n</i> = 48 (%)
Single pathogen	25 (52)
2 pathogens	15 (29)
3 pathogens	7 (15)
4 pathogens	2 (4)
Pathogens <sup>a</sup>	
Gram positive	
MRSA	22 (45.8)
VRE	14 (29)
MSSA	2 (4)
<i>Streptococcus anginosus</i>	2 (4)
<i>Streptococcus agalactiae</i>	1 (2)
Gram negative	
<i>E. coli</i>	17 (35)
<i>Acinetobacte baumannii</i>	7 (14)
<i>E. coli</i> ESBL	5 (10.4)
<i>E. coli</i> KPC	4 (8)
<i>Klebsiella</i> ESBL	2 (4)
<i>Klebsiella</i> KPC	1 (2)
<i>Serratia</i> ESBL	1 (2)
<i>Enterobacter</i> sp	1 (2)
<i>Morganella</i> sp	1 (2)
<i>Achromobacter</i> sp	1 (2)
<i>Stenotrophomonas</i> sp	1 (2)
<i>Bacteroides</i> sp	1 (2)

MRSA methicillin-resistant *Staphylococcus aureus*, VRE vancomycin-resistant enterococci, MSSA methicillin-susceptible *Staphylococcus aureus*, ESBL extended-spectrum beta-lactamase, KPC *Klebsiella pneumoniae* carbapenemase-producing

<sup>a</sup> More than one pathogen was isolated in almost half of infections; percentages reflect this

**Table 5** Clinical and safety outcomes of 50 patients treated with eravacycline

Clinical outcomes	<i>N</i> (%)
Clinical resolution	47 (94)
Clinical failure	3 (6)
Secondary outcomes	Yes/ <i>n</i> (%)
<i>Clostridium difficile</i> infection	
2 weeks post therapy	0
1 month post therapy	1 <sup>a</sup> (2)
Treatment failures	
Required antibiotics	2 (4)
All-cause readmission	2 (4)
Readmission with infection in 30 days	1 <sup>b</sup> (2)
Safety	
Adverse events	
Nausea	2 (4)
Mortality	0
Discontinuation of eravacycline	0

<sup>a</sup> Patient had a history of five recurrences of CDI with management with bezlotoxumab and multiple fecal microbiome transplants

<sup>b</sup> Due to VRE liver abscess

the majority of infections treated in their real-world cohort were beyond the approved intraabdominal infections.

In all three studies, no cases of *C. difficile* were reported post-eravacycline treatment, and the most common adverse events were gastrointestinal-related events (nausea) and rash.

Overall eravacycline has been examined in 77 patients in these three studies with a good clinical cure rate in a series of complex sick patients, some of whom required ICU management.

Fifty patients were enrolled in our real-world study of eravacycline in the US. The range of infections treated in this study reflected the typical types of infection that may be candidates for outpatient antibiotic therapy (OPAT)



**Table 6** Characteristics and outcomes of clinical failure patients

Patient	Culture	Infection	Comorbidities	Readmission related to infection	All-cause readmission	Subsequent antibiotics
1	ESBL <i>E. coli</i> , ESBL <i>K.pneumonia</i> , VRE	Liver abscess	ESLD, PVD, HIV	Yes	Yes	Yes
2	MRSA	Empyema	HTN, HLD, COPD	No	Yes	Yes
3	<i>E. coli</i> , MRSA	Puncture wound on foot	DM	No	No	No

*ESBL* extended-spectrum beta-lactamase, *VRE* vancomycin-resistant enterococci, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ESLD* end-stage liver disease, *PVD* peripheral vascular disease, *HIV* human immunodeficiency virus, *HTN* hypertension, *HLD* hyperlipidemia, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus

such as pneumonia, diabetic foot infections in addition to a variety of intraabdominal infections. Only three ( $N = 50$ ) patients experienced a clinical failure: one liver abscess due to ESBL *E. coli*, ESBL *Klebsiella* and VRE, one empyema due to MRSA and one puncture wound in a diabetic patient yielding MRSA and *E. coli*.

As this was a retrospective observational study using patient electronic records, there are potential weaknesses related to the design; there is no control group treated with alternative antibiotics, so findings can suggest eravacycline's efficacy, but not causal effect. Additionally, there was no way to establish objective microbiologic outcomes, and there is no reporting of follow-up culture data. Strengths of this study are that it provides insight into the real-world application and safety of eravacycline in a variety of infections and among patients with complex comorbidities.

Clinical efficacy with no subsequent positive microbiology suggested that eradication occurred with a range of pathogens including MRSA, *E. coli* including ESBL- and KPC-producing strains, VRE, a range of Enterobacteriaceae and *Acinetobacter* species. This is likely a result of accurate dosing of 1.5 mg/kg q24 given over an hour to achieve an AUC/MIC appropriate for this range of commonly encountered pathogens. Although only one anaerobic organism was isolated, a *Bacteroides* species, it was

presumed to be eradicated based on a positive clinical outcome.

## CONCLUSION

The ability to utilize new drugs requires the relevant data be derived from the daily clinical or real-world setting. The routine randomized controlled trials are conducted for regulatory approval under very restricted conditions in terms of the type of patients and infections treated. Investigators study tightly defined patient groups for various reasons [24]. However, these studies often exclude the very patient type managed each day: those with multiple comorbidities, concomitant medications, different social or demographic groups and often the older individual. Real-world evidence provides information for the formulary members, physicians and pharmacists to make assessments of new compounds usually in indications not covered by the FDA label.

In this study it was notable that 20 patients reported *C. difficile* in the prior 12 months, 13 in the previous 6 months and 7 in the 1 month prior to eravacycline (Table 1), and post-treatment there were no *C. difficile*-positive patients at 2 weeks; at 30 days post-therapy only 1 patient was *C. difficile* positive at 30 days (had been negative at 2 weeks) (Table 5). This individual had reported CDI prior to eravacycline therapy. Tigecycline has been reported to be

effective against *C. difficile*, but is associated with a variety of adverse events [25, 26], whereas only two AEs were reported in our study, and they did not result in discontinuation of eravacycline.

In the seven patients who reported CDI in the month pre-therapy, eravacycline was associated with eradication of CDI as these patients were not CDI positive in the follow-up periods; it is plausible that this is due to the low MIC of *C. difficile* to eravacycline ( $\leq 0.1$  mg/l). However, the single case of CDI at 30 days post-therapy had been infected in the prior 12 months, suggesting long-term colonization.

Given its broad spectrum against clinically relevant pathogens, including tetracycline-resistant and ESBL and KPC strains, eravacycline has potential as an empiric therapy at the higher dose of 1.5 mg/kg in serious infections with the added benefit of single daily dosing, which enables it to be used in the outpatient setting (OPAT), providing high levels of clinical success in a challenging group of patients with few side effects.

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Fliegelman, Michael Anderson, Vishal Didwania, Alice Han, Kairav Shah, Vishnu Chundi, David Hines, Ingrid Roig and Apoorv Kalra have nothing to declare.

**Compliance with Ethics Guidelines.** The study was approved by the Western Institutional Review Board (Reference No. 20192083) and was performed in accordance with the declaration of Helsinki.

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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