

# MAD-ID Newsletter

Winter 2019



**MAD-ID**  
MAKING A DIFFERENCE  
IN INFECTIOUS DISEASES®

Volume 8: Issue 4

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## Antimicrobial Resistance and Public Health

Responding to the threat posed by antimicrobial resistance (AMR) requires a broad approach with stakeholders representing diverse perspectives. The Stakeholder Forum on Antimicrobial Resistance (S-FAR), convened in 2014 by IDSA, is a consortium of organizations representing health professional, patient/consumer, public health, research, industry, and other groups. MAD-ID is a member of S-FAR. We support S-FAR through co-signing letters to government officials and promoting national and global AMR efforts. Learn more about S-FAR at [www.s-far.org](http://www.s-far.org).

Recently, S-FAR commissioned a US public opinion survey that was shared during Antibiotic Awareness Week. Over 80% of Americans are concerned about antibiotic resistance. Across the political spectrum, nearly two-thirds believe that the federal government should increase support for initiatives and investment to address antibiotic resistance. While this public support is encouraging, the findings also highlight needs for more education about the consequences of antibiotic use. To read more about the public opinion survey, visit [www.researchamerica.org/amrsurvey](http://www.researchamerica.org/amrsurvey).

## 2019 MAD-ID Conference Agenda

The 22<sup>nd</sup> annual MAD-ID meeting will be held May 8<sup>th</sup> – 11<sup>th</sup> in Orlando, Florida at the Rosen Centre Hotel. Register by April 7<sup>th</sup> for early-bird rates.

See mad-id.org for more information and updates.

### Wednesday, May 8

- 4:00 – 6:00 Workshops (choose 2 of 4)
- The AMR Challenge: how to meet the challenge at your institution  
*Melinda Neuhauser, PharmD, MPH*
  - Effective implementation strategies and science  
*Elizabeth Dodds-Ashley, PharmD, MHS*
  - Formulary management strategies in antimicrobial stewardship  
*Monica Mahoney, PharmD*
  - Developing skills for stewardship leaders  
*Kerry Laplante, PharmD*

### Thursday, May 9

- 8 – 10:00 Workshops (choose 2 of 4)
- PK/PD applications in stewardship  
*David Nicolau, PharmD*
  - The business of stewardship: Budgets and business plans  
*Elizabeth Dodds-Ashley, PharmD, MHS*
  - Know your data: Designing electronic data queries in the EHR for ASPs  
*Makoto Jones, MD, MS*
  - Start with a strong handshake: Effective stewardship at the bedside  
*Lisa Davidson, MD, MS*
- 10:30 – 11:45 Keynote: New Frontiers in Antimicrobial Stewardship  
*Tim Jenkins, MD*

Sign up for workshops in advance to reserve your seat. Space is limited in individual sessions.

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## Top 5 reasons to attend MAD-ID

- 1 Get inspired!** Draw new ideas from a conference 100% dedicated to antimicrobial stewardship!
- 2 Skill development.** Learn from experts in hands on workshops and take home something you can apply.
- 3 Networking.** The conference is planned to give you time to meet like-minded people and have a chance to interact with renowned speakers
- 4 Share your results.** Poster presentations at MAD-ID highlight important stewardship interventions from people like you.
- 5 Cost-effective.** What other conference offers 18 hours of live CE on topics you care about for under \$600.

## 2019 MAD-ID Conference Agenda, *continued from page 2*

### Thursday, May 9

#### Plenary Sessions

- 1:30 – 3:00 Antibiotic use reporting and SAAR: Current status and what to expect  
*Melinda Neuhauser, PharmD, MPH*  
Using regulations and policies to improve your stewardship program  
*David Hyun, MD*
- 3:30 – 5:00 Long Term Care Stewardship  
*Kerry LaPlante, PharmD*  
Developing Stewardship Goals and Strategies for Nurses  
*Rita Olans, NP, CPNP-PC, APRN-BC*
- 5:00 – 6:30 Scientific Poster Session

### Friday, May 10

#### Plenary Sessions

- 8:00 – 9:30 Antibiotic Use and Stewardship in Primary Care/Urgent Care;  
*Jeffrey Gerber, MD, PhD*  
Point of Care Diagnostic Testing, the Next Frontier for ASPs?;  
*Robin Patel, MD*
- 10:00 – 11:30 Short Course Therapy for Common Infections  
*Monica Mahoney, PharmD*  
Optimizing therapy for Gram-Negative Bacteremia  
*Lisa Davidson, MD, MS*
- 1:30 – 3:00 Behavior Change Interventions to Improve Outcomes  
*Jeffrey Gerber, MD, PhD*  
Patient Stories that can change Practice  
*Steffanie Strathdee, PhD*
- 3:30 – 5:00 New Gram-Negative Agents  
*Jason Gallagher, PharmD*  
New Gram-Positive Agents  
*David Nicolau, PharmD*

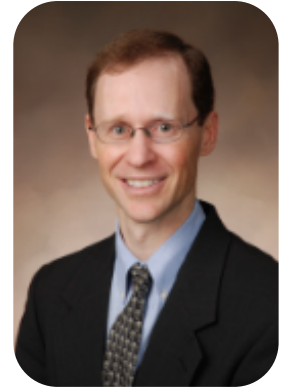
### Saturday, May 11

#### Plenary Sessions

- 8:00 – 9:30 Stewardship News for the Micro Lab – New Tests  
*Robin Patel, MD*  
Practical Interventions with Micro Lab  
*Jason Gallagher, PharmD*
- 10:00-11:30 Infections associated with the opioid epidemic  
*Thomas File, MD, MSc*  
What did you miss at the ID meetings this year?  
*Timothy Jenkins, MD*
- 11:30-12:30 *Meet the Professors*

## MAD-ID Keynote, Tim Jenkins: The Future of Stewardship

Antimicrobial stewardship has evolved significantly since the 2007 publication of the Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship. Not only have those guidelines been revised and updated, the CDC's Core Elements of Antimicrobial Stewardship have expanded from acute care settings to be adapted to nursing homes, outpatient settings, and small and critical access hospitals. Stewardship programs face new opportunities and challenges to provide the best care for patients. As we look to the future of stewardship, MAD-ID has invited Tim Jenkins to share his perspectives and predications during the 2019 keynote presentation.



The learning objectives for this session will be:

- Discuss progress to date in the development and implementation of antimicrobial stewardship strategies
- Identify challenges and barriers associated with current antimicrobial stewardship strategies
- Discuss future frontiers and novel approaches to antimicrobial stewardship

Dr. Jenkins is currently the Director of the Antimicrobial Stewardship Program at Denver Health. His complete biography was shared in the Fall 2018 issue of the newsletter. We hope you will be able to join us for this exciting session.

## Did you know? MAD-ID 2019 will include six presidents of SIDP

You may already know that two of MAD-ID's directors, Dr. Bosso and Dr. Rybak, are past presidents of the Society of Infectious Diseases Pharmacists (SIDP). At this year's MAD-ID conference they will be joined by four other SIDP presidents as presenters. We are happy to have the opportunity to feature these esteemed colleagues.



Kerry LaPlante, PharmD  
Professor of Pharmacy,  
University of Rhode Island  
Adjunct Professor of Medicine,  
Brown University



Jason Gallagher, PharmD  
Clinical Professor,  
Temple University  
School of Pharmacy



Melinda Neuhauser, PharmD, MPH  
Pharmacist and Acute Care Lead  
Office of Antibiotic Stewardship  
Centers for Disease Control and  
Prevention



Elizabeth Dodds-Ashley, PharmD, MHS  
Associate Professor of Medicine  
Division of Infectious Diseases and  
International Health  
Duke University

## Important News from MAD-ID

- **We are going (mostly) paperless!** After you register for this year's annual meeting, be on the lookout for information on how to access meeting materials using the app. The meeting app will be accessible from mobile devices and the web.
- **Submit your abstract for presentation at this year's meeting!** The deadline is April 5<sup>th</sup>, 2019. Instructions and submission portal can be found online. <https://mad-id.org/2019-mad-id-annual-meeting/abstracts-posters/>
- **Trainee travel grants available!** Once again, MAD-ID will be offering limited travel grants to students, residents, or fellows presenting research at the annual meeting. Details available here <https://mad-id.org/2019-mad-id-annual-meeting/id-resident-fellow-program/> And new this year we are offering registration discounts for resident/program director pairs!
- **The Basic Antimicrobial Stewardship Training Program** has been updated. If you've already completed basic ASP training, consider recommending it to one of your colleagues. Core and elective modules are available and include CE for pharmacists, physicians and nurses.

## MAD-ID Research Network: Call for Proposals

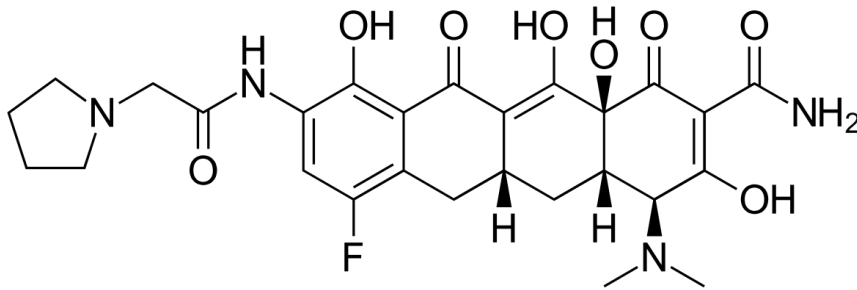
The MAD-ID Research Network is soliciting applications for proposals designed to advance the practice of and/or demonstrate the value of antimicrobial stewardship. Proposals to be considered include a variety of experimental, observational or quasi-experimental designs. The successful proposal will be an innovative application that advances the science and practice of antimicrobial stewardship. Proposals that demonstrate the impact of a stewardship intervention will be preferred.

Applications to this request for proposals should address one or more of the following topics and be aligned with the mission of MAD-ID. Only members of MAD-ID and the research network are eligible.

- Reducing antimicrobial resistance
- Improving patient safety
- Improving patient outcome(s)
- Applying antimicrobial stewardship in novel settings

### To apply

- Visit [mad-id.org](https://mad-id.org) to download the complete request for proposals, instructions, and eligibility requirements. <https://mad-id.org/mad-id-sponsored-antimicrobial-stewardship-research-request-for-proposals/>
- Submit a letter of intent by February 15<sup>th</sup>
- Selected proposals will be invited to submit a full proposal due April 1<sup>st</sup>.



## Eravacycline: A novel fluorocycline

Kyle C. Molina, Pharm.D., Sophia Bonnin, Pharm.D., Vanthida Huang, Pharm.D., FCCP

**Disclosures:** The authors have no conflicts of interest to disclose related to this learning activity.

### Learning Objectives:

At the end of this activity, learners will be able to:

1. Recognize the treatment indication and spectrum of activity of eravacycline
2. Identify the structural modifications to the tetracycline pharmacophore resulting in eravacycline
3. Describe the FDA approved dose of eravacycline for healthy patients and those with severe hepatic impairment
4. Differentiate the findings of the clinical trials between eravacycline in the treatment of complicated intra-abdominal infection and complicated urinary tract infection

### Introduction

Antimicrobial resistance has emerged as one of the major threats to global public health. A recent study suggests that multidrug-resistant (MDR) infections are associated with up to 162,044 deaths annually both in- and outpatient settings in the United States.<sup>1</sup> Complicated intra-abdominal infection (cIAI) represents a significant source of MDR organisms (MDROs).<sup>2</sup> These infections are typically polymicrobial and major pathogens consist of gastrointestinal flora, such as *Enterobacteriaceae*, *Streptococci*, and anaerobes. The emergence of drug resistance among common cIAI pathogens such as extended-spectrum  $\beta$ -lactamase (ESBL) producing organisms, carbapenem-resistant *Enterobacteriaceae* (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococci* (VRE) has limited the effective armamentarium. Therefore, new treatment options with broad-spectrum activity against a host of organisms, including activity against resistant phenotypes and genotypes, are necessary to combat the growing threat of antimicrobial resistance.

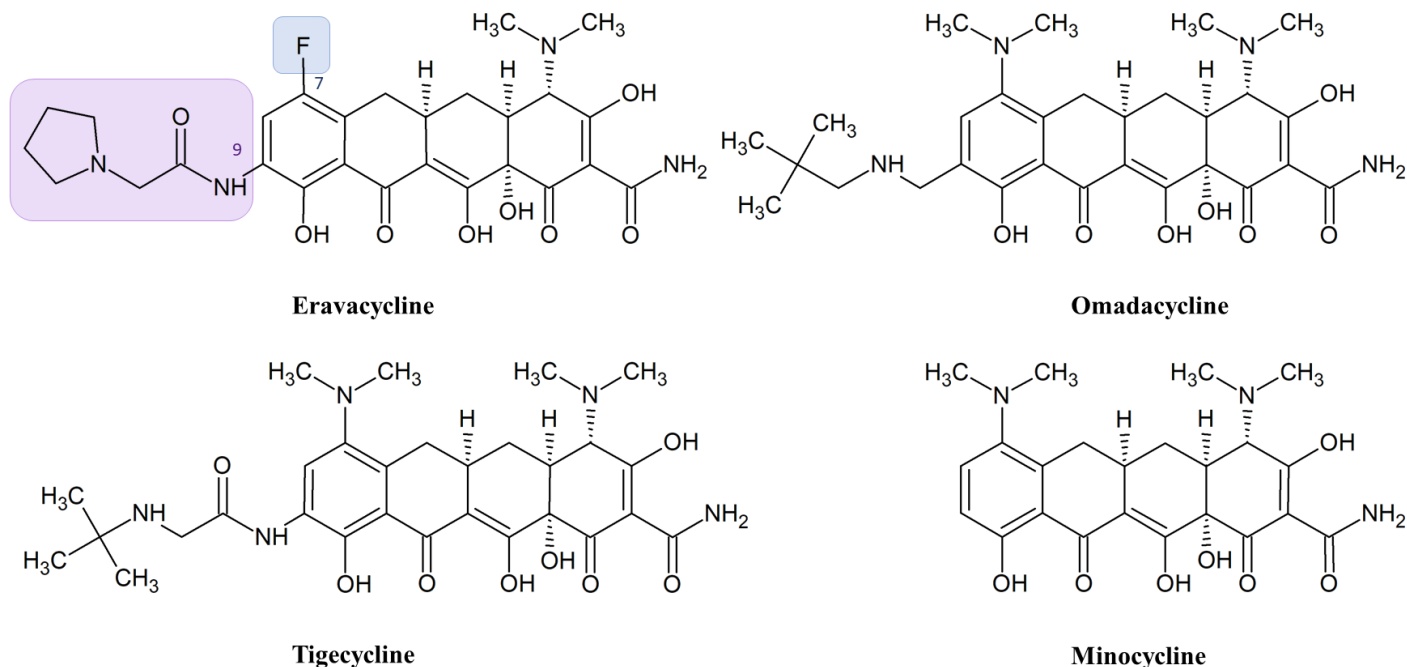
Eravacycline is a novel, fully synthetic, broad-spectrum fluorocycline belonging to the tetracycline class of antibiotics.<sup>3</sup> To address the unmet medical need in treatment options for MDROs, eravacycline was granted approval by the Food and Drug Administration (FDA) for cIAI in August of 2018 after receiving fast track designation as a Qualified Infectious Disease Product (QIDP). Hence, we will review eravacycline in regard to the clinical safety and efficacy, as well as spectrum of activity.

### Structure and Mechanism of Antimicrobial Activity

The tetracycline pharmacophore has been gradually elucidated by a series of structure-activity relationships (SAR) studies.<sup>4,5</sup> Although modifications to the “southeast” pharmacophore interfere with ribosomal binding, modifications to the “northwest” region, particularly at C-7 and C-9 of the tetracycline D-ring, cause no interference with ribosomal binding and enhance antibacterial activity.<sup>5</sup> Therefore, modifications to these sites have increasingly become the target for the development of new tetracycline derivatives.

Eravacycline (formerly TP-434) is a fully synthetic, broad-spectrum fluorocyclic antimicrobial structurally designed to overcome common tetracycline resistance mechanisms. A number of structural similarities exist between eravacycline and the related glycylicycline antibiotic, tigecycline (**Figure 1**). However, eravacycline has two notable substitutions at the tetracycline D-ring. At the C-7 position, a fluorine substitution provides enhanced electronegativity which influences the intrinsic antibacterial potency.<sup>5</sup> The pyrrolidinoacetamido addition at the C-9 position enhances intrinsic antibacterial potency and improves activity against resistant pathogens.<sup>5</sup> Taken together, these modifications result in significant alterations in antibacterial potency, and physicochemical and pharmacokinetic–pharmacodynamic (PK/PD) properties compared to earlier tetracycline derivatives.

**Figure 1: Chemical structures of tetracycline class antibiotics**



Eravacycline exerts its antimicrobial activity through reversible binding to the bacterial ribosome 30S subunit. This action causes blockade of the entry of aminoacyl tRNA molecules and consequently prevents incorporation of amino acid residues into peptide chains. Time-kill analyses have shown that this mechanism produces bacteriostatic antimicrobial activity for eravacycline against *S. aureus*, *E. faecalis*, and the majority of Gram-negative pathogens. Isolate specific bactericidal activity has been observed against subsets of *Enterobacteriaceae* including *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter Baumannii*.<sup>6</sup>

## Microbiology

Eravacycline has demonstrated significant broad-spectrum *in vitro* activity against Gram-positive, Gram-negative, and anaerobic organisms. One study assessed the activity of eravacycline against over 200 clinical isolates collected during a Phase II trial of eravacycline for cIAI.<sup>7</sup> In this analysis, the 90% minimum inhibitory concentration (MIC<sub>90</sub>) ranged from  $\leq 0.008$ -2  $\mu\text{g/mL}$  for all species, with little activity against *Pseudomonas aeruginosa* and *Burkholderia cenocepacia* as evidenced by MIC<sub>90</sub> of 32  $\mu\text{g/mL}$  for both species. In general, the spectrum of activity of eravacycline is similar to that of tigecycline, however, there are notable differences in antimicrobial potency.

A global surveillance program evaluated the *in vitro* activity of eravacycline against 4,015 clinical isolates of *Staphylococcus* spp. and *Enterococcus* spp. collected between 2013 and 2015 from over 200 hospitals.<sup>8</sup> The MIC<sub>50/90</sub> of eravacycline against *S. aureus*, including MRSA, were 0.06/0.12  $\mu\text{g/mL}$ . This potency represents up to a 4-fold increase in activity compared to tigecycline and minocycline. Furthermore, eravacycline demonstrated activity against *S. haemolyticus* and *S. epidermidis* with MIC<sub>50/90</sub> values of 0.12/0.5  $\mu\text{g/mL}$ . Eravacycline demonstrated activity against VRE isolates, with MIC<sub>50/90</sub> values of 0.06/0.12  $\mu\text{g/mL}$  and 0.06/0.06  $\mu\text{g/mL}$  for *E. faecalis* and *E. faecium*, respectively. When compared to other tetracyclines, eravacycline demonstrated up to 4-fold greater activity than tigecycline, 64-fold greater activity than minocycline, and a minimum of 8-fold greater activity than vancomycin against tested *Enterococci* spp. Zhanel et al. demonstrated a favorable activity of eravacycline against 482 *Streptococci* spp., reporting MIC<sub>90</sub> from 0.015-0.06  $\mu\text{g/mL}$ .<sup>9</sup> Collectively, these data demonstrate the potent activity of eravacycline against Gram-positive organisms.

Eravacycline displays *in vitro* activity against a variety of Gram-negative organisms (**Table 1**). In the 2014-2015 CANWARD surveillance study which collected over 4,000 isolates from 13 Canadian hospitals, eravacycline MIC<sub>90</sub> ranged from 0.5-2  $\mu\text{g/mL}$  against nine species of *Enterobacteriaceae* (n = 2,213).<sup>9</sup> The potency of eravacycline was at least equivalent to and often 2- to 4-fold greater than tigecycline against all species of *Enterobacteriaceae* tested. When stratified by presence of ESBL in *E. coli* and *K. pneumoniae*, the activity of eravacycline was largely unaffected.

Although *in vivo* data are currently scarce, the *in vitro* activity of eravacycline against *A. baumannii* and CRE has been evaluated in several recent studies. Livermore et al. evaluated clinical isolates of *A. baumannii* and CRE from the United Kingdom (n=369); eravacycline demonstrated 2- to 4-fold greater activity compared to tigecycline.<sup>10</sup> Additionally, little relationship was observed between eravacycline MICs and specific carbapenem resistance mechanisms. The MIC<sub>90</sub> of eravacycline and tigecycline were 2- to 4-fold higher for CRE and *A. baumannii* isolates than for the carbapenem-susceptible isolates, with comparable MIC<sub>50</sub> shifts for both agents. Seifert et al. compared the activity of eravacycline with amikacin, colistin, levofloxacin, tetracyclines, and tobramycin against carbapenem non-susceptible *A. baumannii* isolates possessing an acquired OXA or metallo- $\beta$ -lactamase, or up-regulated intrinsic OXA-51-like enzyme.<sup>11</sup> The eravacycline MIC<sub>50/90</sub> were 0.5/1  $\mu\text{g/mL}$ , compared to 1/2, 4/8, 32/ $\geq 64$   $\mu\text{g/mL}$  for tigecycline, minocycline, and doxycycline, respectively. Eravacycline demonstrated the most potent antimicrobial activity toward carbapenem non-susceptible *A. baumannii* among all of the agents tested.

Snydman et al. evaluated the activity of eravacycline against 540 anaerobic clinical isolates, including MDR *Bacteroides* spp. and *Clostridium difficile*, collected in the United States from 2012 to 2015.<sup>12</sup> Eravacycline showed the lowest MIC values against *B. fragilis* (n = 286), including



those resistant to tigecycline, minocycline, meropenem, piperacillin-tazobactam, ampicillin-sulbactam, moxifloxacin, and clindamycin. Potent activity was demonstrated against important Gram-negative anaerobes, as all isolates of *Prevotella* spp. (n = 29) and *Fusobacterium* spp. (n = 20) were inhibited at MIC  $\leq 0.5$   $\mu\text{g/mL}$ . All Gram-positive isolates tested, including *C. difficile*, *Clostridium* spp., *Peptostreptococcus* spp., *Propionibacterium* spp. and *Bifidobacterium* spp., and were inhibited at MIC  $\leq 1$   $\mu\text{g/mL}$ .

**Table 1:** *In vitro* activity of eravacycline and tigecycline against Gram-negative bacilli isolated in Canadian hospital laboratories in 2014 and 2015<sup>9</sup>

Organism/Phenotype (n)	Antimicrobial	MIC Determination ( $\mu\text{g/mL}$ )			
		MIC <sub>50</sub>	MIC <sub>90</sub>	MIC Range	
<i>Escherichia coli</i> , all isolates (1,177)	Eravacycline	0.12	0.5	0.03-2	
	Tigecycline	0.25	0.5	0.12-4	
	ESBL positive (141)	Eravacycline	0.25	0.5	0.06-1
	Tigecycline	0.25	0.5	0.12-1	
ESBL negative (1,036)	Eravacycline	0.12	0.25	0.03-2	
	Tigecycline	0.25	0.5	0.12-4	
<i>Klebsiella pneumoniae</i> , all isolates (381)	Eravacycline	0.25	0.5	0.06-8	
	Tigecycline	0.5	1	0.12-16	
	ESBL positive (21)	Eravacycline	0.5	2	0.25-2
	Tigecycline	0.5	2	0.5-4	
ESBL negative (360)	Eravacycline	0.25	0.5	0.06-8	
	Tigecycline	0.5	1	0.12-16	
<i>Klebsiella oxytoca</i> (88)	Eravacycline	0.25	0.5	0.06-1	
	Tigecycline	0.25	0.5	0.12-4	
<i>Enterobacter cloacae</i> (175)	Eravacycline	0.5	1	0.06-8	
	Tigecycline	0.5	1	0.12-8	
<i>Enterobacter aerogenes</i> (33)	Eravacycline	0.25	0.5	0.12-1	
	Tigecycline	0.5	1	0.25-1	
<i>Proteus mirabilis</i> (91)	Eravacycline	1	2	0.5-4	
	Tigecycline	4	8	0.5-8	
<i>Serratia marcescens</i> (83)	Eravacycline	1	2	0.5-8	
	Tigecycline	1	2	1-4	
<i>Morganella morganii</i> (20)	Eravacycline	1	2	0.12-2	
	Tigecycline	1	2	0.12-4	
<i>Citrobacter freundii</i> (19)	Eravacycline	0.25	2	0.12-2	
	Tigecycline	0.5	2	0.25-4	
<i>Stenotrophomonas maltophilia</i> (118)	Eravacycline	1	4	0.24-16	
	Tigecycline	1	4	0.24-16	
<i>Acinetobacter baumannii</i> (28)	Eravacycline	0.06	0.5	0.03-1	
	Tigecycline	0.25	2	0.12-4	

## Mechanisms of Resistance

Extensive use of tetracyclines has contributed to the spread of resistance mechanisms among clinically significant organisms, limiting the utilization of older generation of tetracyclines. Mobile genetic elements carrying tetracycline resistance genes facilitate the rapid dissemination of several mechanisms including tetracycline efflux, ribosomal protection proteins (RPP), and ribosomal modification.<sup>13</sup>

Several resistance genes among a variety of bacteria have been identified which confer resistance to eravacycline. The activity of tetracycline was minimally affected against isogenic *E. coli* expressing major tetracycline-specific resistance genes (*tet(A)*, *tet(B)*, *tet(K)*, *tet(M)*).<sup>14</sup> However, in the presence of *tet(X)* eravacycline MIC was elevated from 0.063 µg/mL to 4 µg/mL. In *S. aureus*, expression of *MepA* (MDR efflux pump) increased the MIC of eravacycline from 0.004 µg/mL to 0.016 µg/mL.<sup>7</sup> In *A. baumannii*, expression of the *adeB* efflux gene has been correlated to elevated MICs.<sup>15</sup> In *Cutibacterium acnes*, a 16S rRNA G1058C mutation has been demonstrated to confer a 23S ribosomal mutation, increasing eravacycline MIC values to 1 µg/mL from 0.063 µg/mL.<sup>14</sup> Among *K. pneumoniae* isolates, *OqxAB* and *MacAB* efflux pumps and the transcriptional regulator *RamA* are suggested to be involved in resistance and heteroresistance to eravacycline.<sup>16</sup>

## Pharmacokinetics and Pharmacodynamics

The PK profile of eravacycline has been well characterized in several studies. Yue et al. assessed the PK of intravenous (IV) eravacycline in single- and multiple-ascending-dose studies in healthy subjects.<sup>17</sup> Intravenous eravacycline demonstrated linear pharmacokinetics which were described by a four-compartment model. The mean steady-state volume of distribution ( $V_{ss}$ ) was 4.2 L/kg, the mean terminal elimination half-life ( $t_{1/2}$ ) was 48 h, and the mean total clearance (CL) was 13.5 L/h. Atypical non-linear, concentration-dependent protein binding has been observed with free fraction of eravacycline ranging from 10% to 20% at concentrations of 10 µg/mL to 0.1 µg/mL.<sup>18</sup> As eravacycline is primarily metabolized hepatically, only ~16% of the parent compound is excreted unchanged in the urine.<sup>17</sup> A Phase I, open-label study demonstrated favorable concentrations of eravacycline in epithelial lining fluid and alveolar macrophages, underscoring the potential for use in patients with respiratory infections.<sup>19</sup>

The pharmacodynamic parameter which best predicts clinical efficacy of tetracyclines appears to be the free area under the curve (AUC) to MIC ( $fAUC/MIC$ ) ratio. Using a neutropenic murine thigh infection model, Zhao et al. demonstrated that  $fAUC/MIC$  was the PK/PD parameter that best correlated with efficacy ( $R^2$  0.80).<sup>20</sup> Furthermore, the mean  $fAUC/MIC$  associated with net stasis and 1-log kill endpoint were  $27.97 \pm 8.29$  and  $32.60 \pm 10.85$ , respectively.

## Dosage and Administration

The FDA approved dose of eravacycline for the treatment of cIAI in patients with normal hepatic function is 1 mg/kg every 12 hours administered as an intravenous infusion over 60 minutes. In patients with severe hepatic impairment (Child Pugh C), the dosing interval of eravacycline is extended to every 24 hours after two doses have been administered.<sup>3,21</sup> As eravacycline is only minimally excreted in the urine, no dosing adjustment is required for patients with renal impairment.<sup>3</sup> In patients using a concomitant strong CYP3A inducer, eravacycline should be dosed as 1.5 mg/kg IV every 12 hours. Notably, the oral formulation of eravacycline has not received FDA approval and at least some data has suggested that this formulation contributed to the lack of efficacy seen in the cUTI trials.<sup>22</sup> It is unclear at this time whether continued clinical development of the oral formulation will be pursued.

## Clinical Efficacy

The Investigating **Gram-Negative Infections Treated with Eravacycline (IGNITE)** phase III clinical program has investigated the clinical efficacy of eravacycline in four clinical trials for cUTI and cIAI (**Table 2**).

**Table 2: Phase III Clinical Trials of Eravacycline**

Trial (Indication)	Treatment arms	micro-ITT population (n)	Clinical Cure micro-ITT (% ERV vs. Comparator [Difference (95% CI)])		
			EOT	TOC	FU
IGNITE1 (cIAI)	ERV 1 mg/kg IV q12h	446	91.4 vs. 93.4	86.8 vs. 87.6	--
	ERT 1 g IV q24h		[-2.0(-7.2,3.0)]	[-0.80(-7.1,5.5)]	
IGNITE2 (cUTI)	ERV 1.5 mg/kg IV q24h followed by 200 mg PO q12h	600	86.6 vs. 81.1	--	60.4 vs. 66.9
	LEV 750 mg IV q24h followed by 750 mg PO q24h		[5.5(-0.5,11.4)]		[-6.5(-14.1, 1.2)]
IGNITE3 (cUTI)	ERV 1.5 mg/kg IV q24h	823	84.8 vs. 94.8 (EOI)	68.5 vs. 74.9	--
	ERT 1 g IV q24h		[-10(-14.1, -6)]	[-6.5(-12.6, -0.3)]	
IGNITE4 (cIAI)	ERV 1 mg/kg IV q12h	400	92.8 vs. 94.1	90.8 vs. 91.2	87.2 vs. 90.2
	MER 1 g IV q8h		[-1.3(-6.5,3.7)]	[-0.5(-6.3,5.3)]	[-3.1(-9.5,3.2)]

EOI= end of infusion; EOT = end of therapy; ERT = ertapenem; ERV = eravacycline; FU = follow up; IV = intravenous; MER = meropenem; micro-ITT = microbiological intent-to-treat; PO = oral; TOC = test of cure

### IGNITE1

The IGNITE1 was a Phase III, randomized, double-blind, multicenter, noninferiority trial of eravacycline for the treatment of cIAI.<sup>23</sup> Adult patients received either eravacycline 1 mg/kg IV every 12 hours or ertapenem 1 gram IV every 24 hours for a minimum of four days. The primary objective was to evaluate clinical response at test-of-cure (TOC) visit to demonstrate noninferiority in the micro-ITT population. A total of 541 patients were randomized, with 270 and 271 randomized to eravacycline and ertapenem, respectively. Of patients randomized, 446 (82.4%) had baseline bacterial pathogens against at least one of which the study drug had *in vitro* antibacterial activity, and therefore were analyzed as the micro-ITT population. Patients in the micro-ITT population displayed similar demographic characteristics across treatment groups. Enrolled patients had a mean age of approximately 55 years, were primarily male (~57%), and had a body mass index of ~28 kg/m<sup>2</sup>. Across all treatment arms, the most common intra/post-surgical diagnoses included total appendicitis, total cholecystitis, gastrointestinal/duodenal perforation, and total intestinal perforation. At TOC, rates of clinical cure were similar between eravacycline and ertapenem groups (86.8% vs 87.6, respectively), meeting the prespecified 10% noninferiority margin. Honore et al. critiqued this study for the exclusion of critically-ill patients, lack of generalizability to resistant pathogens due to the small number of CRE present, and clinical cure rates inconsistent with the spectrum of activity of eravacycline.<sup>24</sup>

### IGNITE2

The IGNITE2 trial was a Phase III, randomized, double-blind, noninferiority trial evaluating the efficacy and safety of eravacycline compared to levofloxacin for the treatment of cUTI in hospitalized patients.<sup>22</sup> The primary endpoint was a composite of clinical cure and microbiologic success with a noninferiority margin of 10% at post-treatment (PT) visit. Adult patients received either eravacycline 1.5 mg/kg once daily or levofloxacin 750 mg IV once daily for three days. After three days of IV therapy, patients were allowed to transition to oral therapy with eravacycline 200 mg twice daily or levofloxacin 750 mg once daily to complete a total of seven days duration of therapy. A total of 600 patients were included in the micro-ITT population: 298 patients in the eravacycline group and 302 in the levofloxacin group. Eravacycline did not achieve noninferiority in responder rate at PT visit in the micro-ITT population [Difference (95%CI) = -6.5(-14.1,1.2)]. Failure to achieve noninferiority highlights potential issues with the rapid transition to the oral formulation of eravacycline. In the subset of patients who received seven days of IV eravacycline a higher response rate was observed, 58.8% compared to levofloxacin 48.2%.

### IGNITE3

The IGNITE3 trial is currently unpublished; therefore, the availability of these data is limited. The IGNITE3 trial was a Phase III, randomized, double-blind, noninferiority trial to evaluate the efficacy and safety of eravacycline compared to ertapenem for the treatment of cUTI.<sup>25</sup> Due to positive clinical response observed in the subset of patients who received longer courses of IV therapy in the IGNITE2 trial, a minimum 5-day duration of IV therapy was chosen for this trial. Adult patients received either eravacycline 1.5 mg/kg IV every 24 hours or ertapenem 1 gram IV every 24 hours for a minimum duration of 5 days, where transition to oral therapy was permissible. The co-primary endpoints were clinical cure and microbiological success in the micro-ITT population at end-of-IV (EOI) treatment visit and at TOC with a 10% noninferiority margin. A total of 831 patients were included in the micro-ITT population: 428 and 403 patients in the eravacycline and ertapenem arms, respectively. Responder rates at EOI visit were 84.8% in the eravacycline arm and 94.8% in the ertapenem arm [Difference (95%CI) = -10(-14.1,6.0%)] with rates at TOC visit of 68.5% and 74.9%, respectively (-6.5% CI -12.6% to -0.3%). Similar to IGNITE2, eravacycline did not achieve noninferiority for the treatment of cUTI.

### IGNITE4

The IGNITE4 trial was a Phase III, randomized, double-blind, noninferiority trial which compared eravacycline to meropenem for the treatment of cIAI.<sup>26</sup> Adult patients received either eravacycline 1 mg/kg IV every 12 hours or meropenem 1 gram IV every 8 hours with 4-14 days duration of treatment. The primary objective was to demonstrate noninferiority in clinical cure rates of the micro-ITT population at the TOC visit, defined as 25-31 days from day 1 of therapy, with a noninferiority margin of 12.5%. Secondary endpoints included clinical and microbiological responses for the micro-ITT, modified ITT (mITT), clinically evaluable, and microbiologically evaluable populations at end-of-treatment, TOC, and follow-up visits.

A total of 400 patients were included in the micro-ITT population of IGNITE4, with 195 patients in the eravacycline arm and 205 patients in the meropenem arm. Patients included were a mean approximate age of 50 years old, primarily male (> 50%), and with an average body mass index of ~ 27 kg/m<sup>2</sup>. The most common intra/post-surgical diagnoses included intra-abdominal abscess, peritonitis, gastrointestinal/duodenal perforation, and complicated appendicitis across treatment arms. For the primary efficacy outcome, cure rates were 90.8% in the eravacycline arm compared to 91.2% in the meropenem arm [Difference (95%CI) = -0.5(-6.3,5.3)]. Clinical cure rates among all

other visits and populations were consistent with those reported in the primary outcome with cure rates of 90.8% to 96.9% in the eravacycline arm and 91.2% to 96.4% in the meropenem arm. Eravacycline met the pre-specified noninferiority margin to meropenem for the treatment of cIAI, further supporting the findings of the IGNITE1 trial.

Analyses of pooled IGNITE1 and IGNITE4 data have been performed which provide further evidence toward the efficacy of eravacycline in cIAI.<sup>27,28</sup> These data underscore the high microbiological eradication and clinical cure observed in *Enterobacteriaceae* spp., consistent with *in vitro* studies. Furthermore, these data support additional clinical investigation into use against MDR Gram-negative pathogens in other infections as favorable microbiological and clinical responses were observed against *Enterobacteriaceae* and *A. baumannii* that were 3<sup>rd</sup>/4<sup>th</sup> generation cephalosporin-resistant, ESBL-producing, or MDROs.

### Safety and Tolerability

In the conducted Phase III trials for cIAI, eravacycline has demonstrated a favorable safety profile. The most frequently reported adverse events were infusion site reactions, nausea, vomiting, and diarrhea.<sup>21</sup> Given the close structural similarity to tigecycline, the prevalence of nausea has been of concern throughout the clinical development of eravacycline. The incidence of nausea in the Phase III cIAI trials in patients receiving eravacycline was 6.5% compared to rates in excess of 20% seen in tigecycline clinical trials. Being structurally similar to tetracycline antibiotics, eravacycline has warnings including tooth discoloration, inhibition of bone growth, among other tetracycline class adverse reactions.

### Conclusion

The recent FDA approval of eravacycline for the treatment of cIAI provides an additional option to the existing antibiotic armamentarium. The enhanced antimicrobial activity against a broad range of pathogens, including MDROs, with a favorable adverse event profile may provide clinical advantage for eravacycline among the tetracyclines. In particular, eravacycline is a potential therapeutic option against difficult-to-treat MDR Gram-negative organisms such as CRE and *A. baumannii*, however, further clinical study is warranted.

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Kyle C. Molina,  
Pharm.D



Sophia Bonnin,  
Pharm.D



Vanthida Huang,  
Pharm.D., FCCP

## About the authors

**Kyle C. Molina**, PharmD, is a PGY-1 pharmacy resident at Scripps Mercy Hospital in San Diego, California

**Sophia Bonnin**, PharmD, is a PGY-1 pharmacy resident at St. Joseph's Hospital and Medical Center in Phoenix, Arizona.

**Vanthida Huang**, PharmD, FCCP, is an Associate Professor at Midwestern University College of Pharmacy-Glendale in Glendale, Arizona. Dr. Huang received her BSPHM and PharmD from Temple University School of Pharmacy. She completed residency at Sarasota Memorial Hospital and Infectious Diseases Pharmacotherapy Fellowship at Wayne State University. Her areas of research include multidrug-resistant gram-positive bacteria and antimicrobial pharmacokinetics and dynamics. Her work has been published in multiple scientific journals including Antimicrobial Agents and Chemotherapy, International Journal of Antimicrobial Agents, and the International Journal of Infectious Diseases.

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The self-assessment quiz that can be found at the end of this article can be completed for 1 CEU of Continuing Pharmacy Education credit. The quiz may be completed online (<http://madidtraining.org/newsletter/>) at no cost for MAD-ID members. Non-members should print and mail the completed quiz, along with a \$15.00 check made payable to MAD-ID to: MAD-ID, 537 Calico Retreat, Mt. Pleasant, SC 29464-2765. Your CE credit will be reported on CPE monitor within 4 weeks of receipt.

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## Self Assessment Questions

(To be completed online (<http://mad-idtraining.org/newsletter/>) or, in the case of non-MAD members, printed and mailed. You must achieve a grade of 80% or better to receive continuing education credit.)

1. Eravacycline shows minimal activity for which of the following organisms? (Objective 1)
  - A. *Acinetobacter baumannii*
  - B. *Escherichia coli*
  - C. *Klebsiella pneumoniae*
  - D. *Pseudomonas aeruginosa*
2. Which of the following modifications to tetracycline pharmacophore enhance the potency and stability of eravacycline against common tetracycline resistance mechanisms? (Objective 2)
  - A. C7-dimethylamino
  - B. C7-pyrrolidinoacetamido group, C9-fluorine
  - C. C7-fluorine, C9-pyrrolidinoacetamido group
  - D. C7-dimethylamino, C9- [[2-(tert-butylamino)acetyl]amino]
3. Which of the following eravacycline regimens is recommended for the treatment of complicated intra-abdominal infections in an otherwise healthy adult patient, not in concomitant with CYP-inducing medications? (Objective 3)
  - A. 1 mg/kg IV every 24 hours
  - B. 1.5 mg/kg IV every 24 hours
  - C. 1 mg/kg IV every 12 hours
  - D. 1.5 mg/kg IV every 12 hours
4. Which of the following regimens is best to initiate for a 50-year-old male with past medical history significant for cirrhosis of the liver (Child Pugh C) who was admitted to the hospital with a diagnosis of complicated intra-abdominal infection? (Objective 3)
  - A. 1 mg/kg IV every 12 x 2 doses, then 1 mg/kg IV every 24 hours
  - B. 1mg/kg IV every 12 hours x 2 doses, then 1.5mg/kg IV every 24 hours
  - C. 1.5 mg/kg every 12 hours x 2 doses, then 1 mg/kg IV every 24 hours
  - D. 1.5 mg/kg IV q12h x 2 doses, then 1.5 mg/kg IV every 24 hours
5. Which of the following clinical trials did eravacycline fail to demonstrate noninferiority to levofloxacin for cUTI? (Objective 4)
  - A. IGNITE1
  - B. IGNITE2
  - C. IGNITE3
  - D. IGNITE4



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Please provide your honest assessment of the value of this learning activity so that we can continue to improve our offerings.

Please indicate your degree of agreement or disagreement with the following statements regarding this learning activity by indicating strong agreement (a), general agreement (b), no opinion (c), mild disagreement (d), or strong disagreement (e):

Criteria	Strong agreement	General agreement	No opinion	General disagreement	Strong disagreement
The information presented was relevant to my practice	a	b	c	d	e
This program/session met the stated learning objectives	a	b	c	d	e
The information was presented in an objective and balanced manner without commercial bias	a	b	c	d	e
The information presented will alter/affect my practice (usefulness)	a	b	c	d	e
The educational materials enhanced my learning	a	b	c	d	e
The learning method was effective	a	b	c	d	e
The learning assessment activity (self-assessment quiz) was appropriate	a	b	c	d	e
The faculty/authors were of appropriate quality	a	b	c	d	e

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