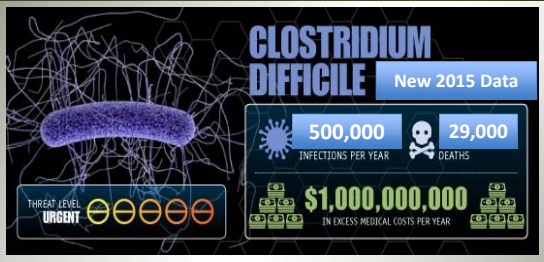
Applying the Latest Approaches in the Management of *C. difficile* Infection and Recurrence

Kevin W. Garey, PharmD, MS, FASHP
Chair, Department of Pharmacy Practice and Translational Research
Professor of Pharmacy Practice
College of Pharmacy
University of Houston
Houston, TX

Objectives

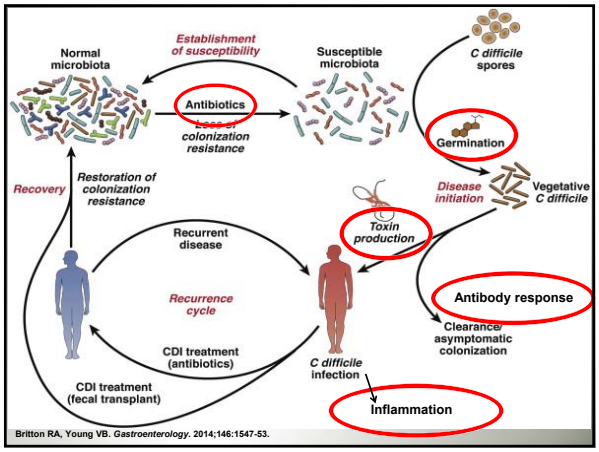
- Assess the role of newer antimicrobial agents as part of the armamentarium in the management of infections caused by *C. difficile*
- Evaluate the utility of novel approaches that reduce the risk of recurrent *C. difficile* infection in high-risk patients

The Impact of *Clostridium difficile* Infections (CDI)



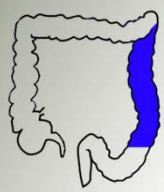
Of patients with CDI given metronidazole or oral vancomycin, 25% will experience recurrent CDI

Source: CDC Report. Antibiotic Resistance Threats in the United States, 2013. Available at: https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.
Lessa CF et al. *NEJM.* 2015;372:825-34.



Britton RA, Young VB. *Gastroenterology.* 2014;146:1547-53.

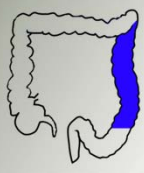
Therapeutic Goals for CDI

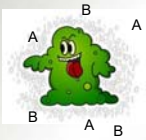


Essential:	Correct dysbiosis	Kill the organism	Adaptive immunity
Optional but nice:	Safe and convenient	Also affects toxins and spores	Short vs. long-term

Adamu BO, Lawley TD. *Curr Opin Microbiol.* 2013;16:596-601.

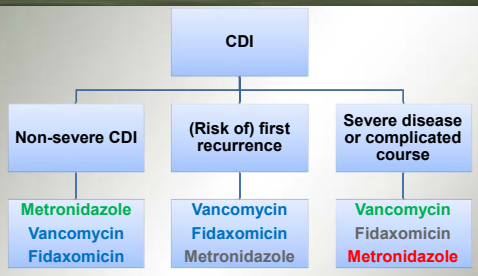
There has Been an Explosion in Treatment Possibilities for CDI





Current:	Probiotics FMT Use narrow-spectrum antibiotics	Metronidazole Vancomycin Fidaxomicin	IVIG Monoclonal antibodies vs. *C. difficile* toxins
Future:	2nd-generation FMT non-tox *C. difficile* M3 Ecobiotics	~~Surotomycin~~ Cadazolid Ridinilazole	Toxoid vaccines

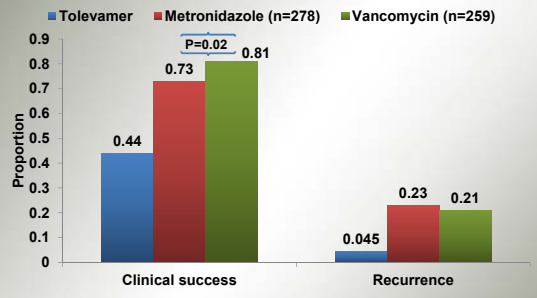
Current European CDI guidelines



Green: strongly supports use; Blue: moderately supports use; Grey: Minimally supports use; Red: recommend to not use

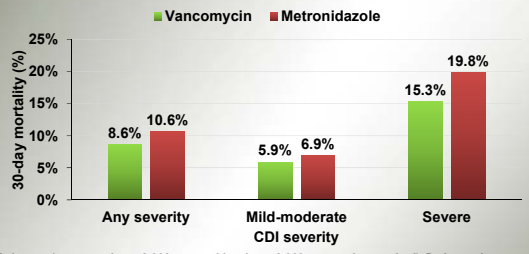
Debast SB, et al. *Clin Microbiol Infect.* 2014;20(Suppl 2):1-26.

More Recently, Metronidazole has been Shown to be Globally Inferior to Vancomycin (Tolevamer Phase III RCT)



Johnson S, et al. *Clin Infect Dis.* 2014;59:345-354.

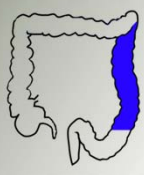
Increased Failure Rate of Metronidazole also Associated with Increased 30-day Mortality

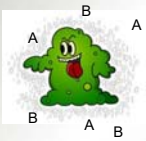


VA dataset (vancomycin: n=2,068; metronidazole: n=8,069 propensity matched). Patients given vancomycin had a significantly lower risk of 30-day mortality (RR: 0.86, 95% CI: 0.74-0.98). No difference in CDI recurrence regardless of disease severity or choice of antibiotic (16.3-22.8%)

Stevens VW, et al. *JAMA Intern Med.* 2017;177:546-53.

Explosion in Treatment Possibilities for CDI Minus 1





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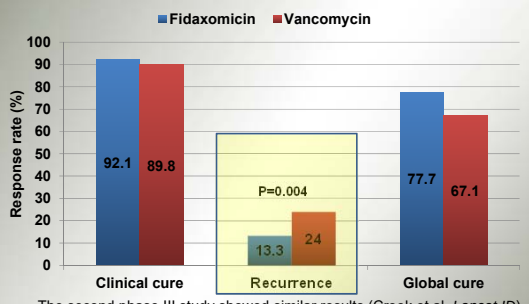
Future:	2nd-generation FMT non-tox *C. difficile* M3 Ecobiotics	~~Surotomycin~~ Cadazolid Ridinilazole	Toxoid vaccines

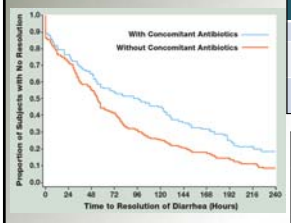
Fidaxomicin: Equal Efficacy as Vancomycin to Cure Patients and Lessens the Risk of Recurrence



The second phase III study showed similar results (Crook et al. *Lancet ID*)

Louie T, et al. *N Eng J Med.* 2011;364:422-310.

Impact of Concomitant Antibiotics on Response to CDI Treatment



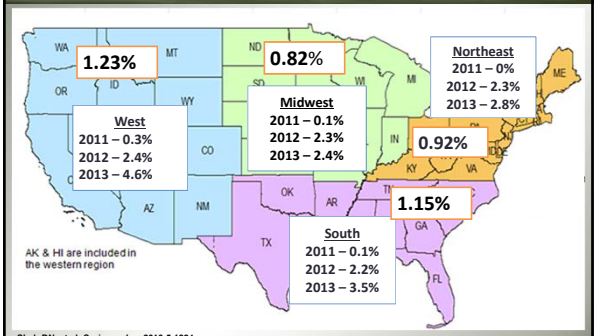
No CA	Fidaxo N=391	Vanco N=416	P
Clinical cure	92%	93%	0.80
Recurrence	12%	23%	<0.001
Sustained response	81%	69%	<0.001

CA	Fidaxo N=90	Vanco N=102	P
Clinical cure	90%	79%	0.04
Recurrence	17%	29%	0.05
Sustained response	72%	59%	0.02

CA = concomitant antibiotics

Mullane KM, et al. *Clin Infect Dis.* 2011;53:440-7.

However, this Drug is Quite Costly: Fidaxomicin Use By Region



Shah DN, et al. *Springerplus.* 2016;5:1224.

We Really Have to Do a Better Job of Using Fidaxomicin Correctly

	Early episodes			Later episodes	Overall (n=102)
	Episode 1 (n=37)	Episode 2 (n=32)	Total (n=69)	Episode ≥ 3 (n=33)	
Mild-Moderate CDI; n(%)	10 (27%)	12 (37.5%)	22 (32%)	N/A	22/69 (32%)
Severe CDI; n(%)	27 (73%)	20 (62.5%)	47 (68%)	N/A	47/69 (68%)
1. FDX monotherapy; n (%)	3 (8%)	4 (12.5%)*	7 (12%)	6 (18%)	13 (13%)
2. Other CDI therapy; n (%)	34 (92%)	27 (84%)	61 (88%)	27 (82%)	88 (86%)
I. Subsequent; n	18	14	32	16	48
II. Subsequent and combination; n	8	6	14	2	16
III. Combination; n	2	1	3	1	4
IV. Unable to categorize; n	6	6	12	8	20
Concomitant non-CDI antibiotics; n (%)	25 (68%)	10 (31%)	35 (51%)	13 (39%)	48 (47%)

Multicenter, 11 hospital chart review study of hospitalized patients with CDI that received fidaxomicin between 2011 and 2013.

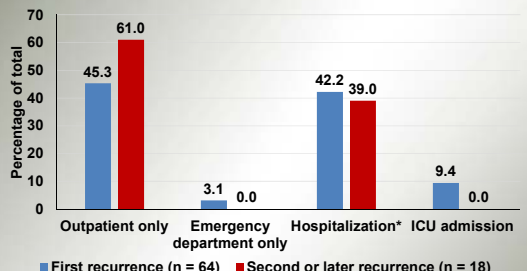
Shah DN, et al. *Springerplus.* 2016;5:1224.

Appropriate Use of Fidaxomicin

- Because of high acquisition cost, fidaxomicin has been reserved for a very select patient population almost always in combination with other anti-*C. difficile* or other antibiotics
- Remember: fidaxomicin's primary MOA is its narrow spectrum of activity preserving host microbiota
- Can the anti-recurrence effect of fidaxomicin offset its high acquisition cost?

Shah DN, et al. *Springerplus.* 2016;5:1224.

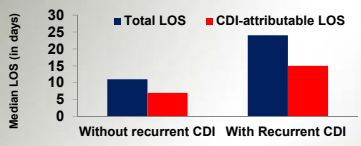
Recurrent CDI is Costly: Healthcare Utilization for Recurrent CDI



*Of disease-attributable readmission, 85% returned to the initial hospital for care

Aitken SL, et al. *PLoS One.* 2014;9(7):e102848.

Increased Healthcare Utilization = Increased Healthcare Costs



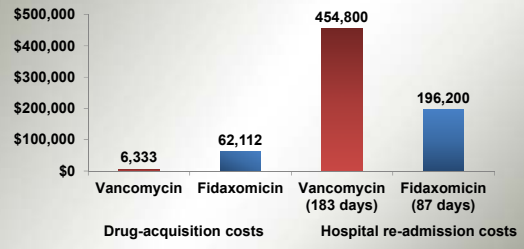
Cost in US dollars; median (IQR)	Without recurrent CDI	With recurrent CDI
CDI pharmacologic treatment*	$60 (23 – 200)	$140 (30 – 260)
CDI-attributable hospitalization^	$13,168 (7,525 – 24,455)	$28,218 (15, 049 – 47,030)
Total hospitalization^	$20,693 (11,287 – 41,386)	$45,148 (20,693 – 82,772)

Shah DN, et al. ICAAC 2014 Poster #K-356, Sat, Sept 6, 2014.

Any Evidence that Fidaxomicin may Reduce these Costs?

Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for select patients.

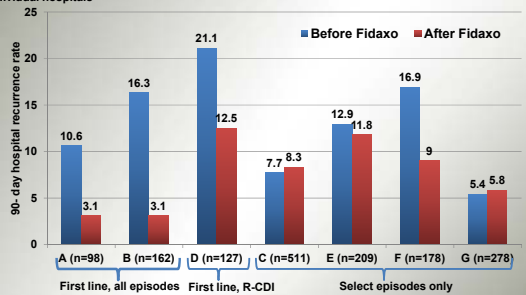
CDI-related re-admissions: Fidaxo: 20.4%; Vanco: 41.3%



Gallagher JC, et al. *Antimicrob Agents Chemother.* 2015;59:7007-10.

Real-world Evidence that Fidaxomicin may Reduce these Costs?

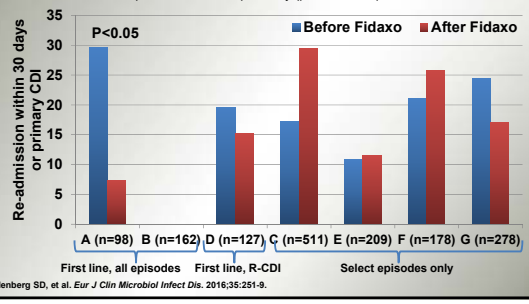
UK, 2012–13: Seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals



Goldenberg SD, et al. *Eur J Clin Microbiol Infect Dis.* 2016;35:251-9.

Real-world Evidence that Fidaxomicin may Reduce these Costs?

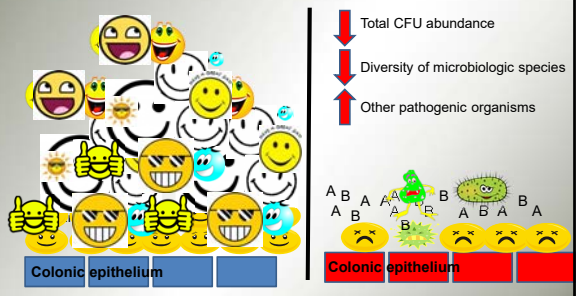
UK, 2012–13 : Seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals. Mortality rates decreased from 18.2% and 17.3% to 3.1% and 3.1% in hospitals A and B, respectively (p<0.05, each)



Goldenberg SD, et al. *Eur J Clin Microbiol Infect Dis.* 2016;35:251-9.

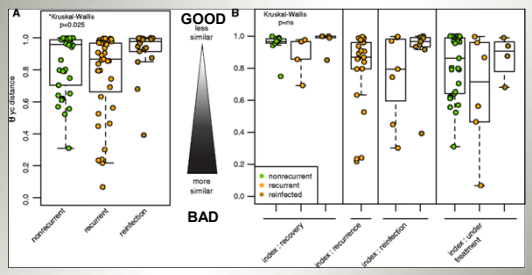
It's Important to Remember that Recurrent CDI is More than about Cost

Microbiome of non-CDI patients vs. CDI patients



The Microbiome "Organ" Continues to be Damaged with Recurrent CDI

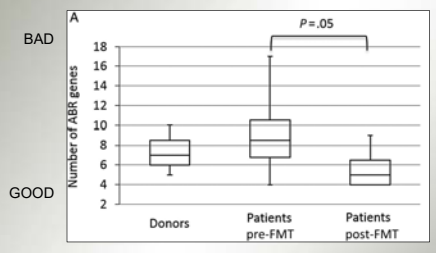
Michigan: 93 patients with CDI. Fecal microbiome diversity during initial infection (A) and during follow-up period. All patients treated with metronidazole or vancomycin.



Seekatz AM, et al. *Genome Med.* 2016;8(1):47.
Available at: https://genomemedicine.biomedcentral.com/articles/10.1186/s13073-016-0298-8.

What Else do We have in our Damaged Microbiome?

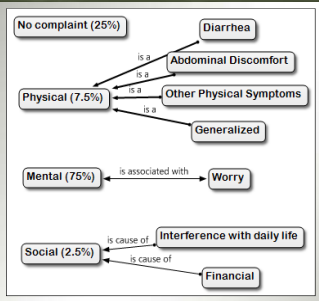
Canada: Number of antibiotic-resistant genes (ABR) present in stool samples from patients with recurrent CDI before and after FMT (n=8)



Jouhten H, et al. *Clin Infect Dis.* 2016;63(5):710-11.

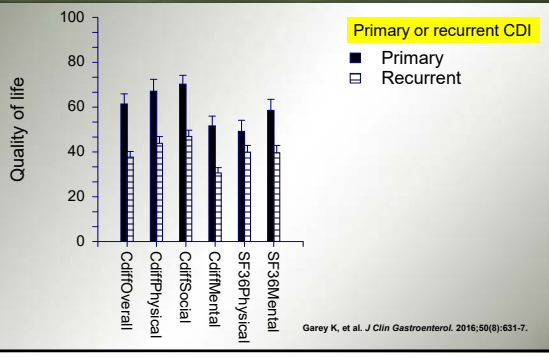
And Last But not Least, the Patient Perspective

The Driver for Decreased QOL is not so Much Physical as a Worry/Anxiety of Transmissibility or Symptom Persistence



Goddu S, Bozorgui S, et al. Presented at ISPOR 20th Annual International Meeting, Philadelphia, PA, May 2015.

Quality of Life (QOL) Goes Down Considerably with Recurrent CDI

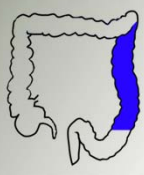


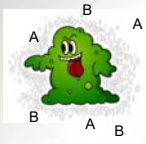
Garey K, et al. *J Clin Gastroenterol.* 2016;50(8):631-7.

Patient Perspective

"It was a little over a year ago I was diagnosed and treated with metronidazole, then treated again in April with vancomycin for it as tested positive again, and am 50 years old and otherwise healthy except for hypertension issues. I think I acquired it as a caretaker for my elderly mother (who has since passed away), and having antibiotics for dental issues. I wouldn't wish this illness on my worst enemy, and it's been a life changer for me."

Explosion in Treatment Possibilities for CDI: Augment Immune Response!





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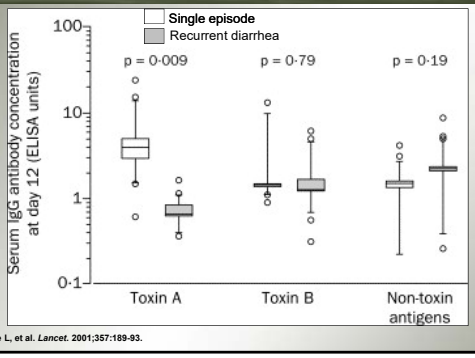
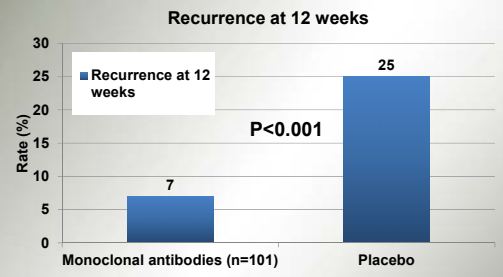
Serum Concentrations of IgG Antibodies Against Toxin A, Toxin B, and Non-toxin Antigens



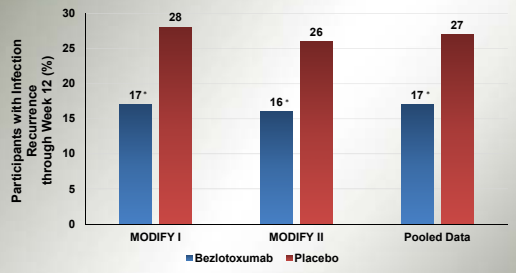
Kyne L, et al. *Lancet.* 2001;357:189-93.

Monoclonal Antibody: Phase II Study



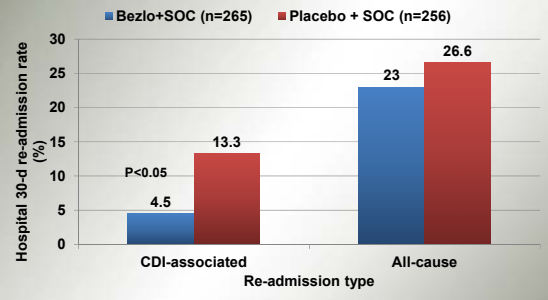
Lowy I, et al. *N Engl J Med.* 2010;362:197-205.

Phase III Studies of Bezlotoxumab: CDI Recurrence



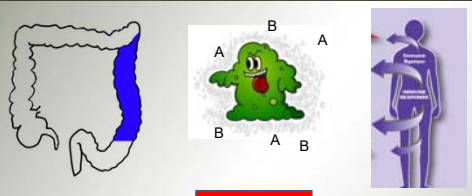
*p<0.001
Wilcox MH, et al. *N Engl J Med.* 2017;376:305-17.

Bezlotoxumab was also Shown to Reduce Hospital Re-admissions (European Population)



Gerding DN, et al. Abstract 2000. Presented at: ECCMID; April 9-12, 2016; Amsterdam.
Wilcox MH, et al. Abstract 1996. Presented at: ECCMID; April 9-12, 2016; Amsterdam.

Explosion in Treatment Possibilities for CDI: Correct Dysbiosis!



Current: Probiotics
FMT
Use narrow-spectrum antibiotics

Vancomycin
Fidaxomicin

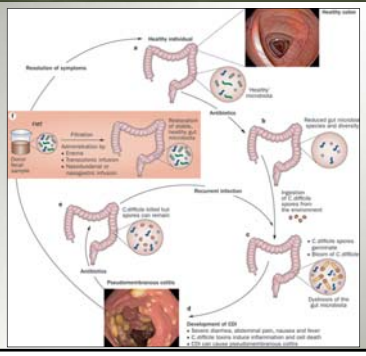
IVIG
Monoclonal antibodies vs. *C. difficile* toxins

Future: 2nd-generation FMT
non-tox *C. difficile* M3
Ecobiotics

~~Surotomycin~~
Cadazolid
Ridinilazole

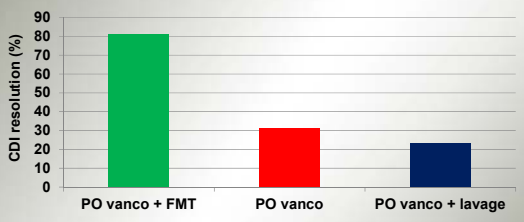
Toxoid vaccines

FMT for Patients with Recalcitrant CDI



Duodenal Infusion of Donor Feces for Recurrent *C. difficile* Infection

RCT of PO vanco + FMT (n=16), PO vanco alone (n=13), or PO vanco + bowel lavage (n=13). Study stopped prematurely due to superiority of FMT.



Resolution: no diarrhea without relapse after 10 weeks

van Nood E, et al. *N Engl J Med.* 2013;368:407-15.

Correction of Dysbiosis will Likely Become Standard Practice in CDI (and beyond). We Will Always Need to Kill the Bug Though!

25 patients with recurrent CDI that were not able to perform FMT. Twenty-one of the 25 patients (84%) remained free of diarrhea during the following 9 months. The 4 patients who relapsed permanently resolved their diarrhea after a conventional 2-week course of oral vancomycin 125 mg 4 times daily followed by a 2-week course of rifaximin 200 mg twice daily. All 4 patients remained symptom-free at 12 months of follow-up.

Antibiotic Time Course	Metronidazole Dose/Frequency		Vancomycin Dose/Frequency		Kefir
Weeks 1-2	250 mg Q 6h		125 mg Q 6h		150 mL TID
Weeks 3-4	750 mg Q 72h		375 mg Q 72h		150 mL TID
Weeks 5-6	500 mg Q 72h	OR	250 mg Q 72h	PLUS	150 mL TID
Weeks 7-8	250 mg Q 72h		125 mg Q 72h		150 mL TID
Weeks 9-15					150 mL TID

Bakken JS. *Clin Infect Dis*. 2014;59:858-61.

Conclusion

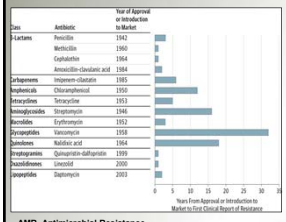
- As long as we live in a world of elderly, hospitalized patients given broad-spectrum antibiotics, CDI is here to stay.
- With a coordinated effort and contemporary epidemiologic techniques, we can likely control and respond to future changes in the pathogenesis of CDI.
- With a little luck and good science, we may also be able to discover new insights into strategies to prevent and control CDI.

Current Therapeutic Options for Antimicrobial-Resistant Gram-Negative Infections

Keith A. Rodvold, PharmD, FCCP, FIDSA
Professor of Pharmacy Practice and Medicine
Colleges of Pharmacy and Medicine
University of Illinois at Chicago
Chicago, IL

Antimicrobial Resistance

Emergence of Antimicrobial Resistance: Time Between Regulatory Approval or Introduction to the Market



AMR, Antimicrobial Resistance

- In USA:
  - AMR organisms cause >2 million infections
  - 23,000 deaths each year (~25,000 in Europe)
  - Estimated $20 billion in excess medical spending each year
- Full global effect of AMR is difficult
- Recent global emergence:
  - USA (carbapenem-resistant *Klebsiella pneumoniae*)
  - India (bacteria with the plasmid-mediated bla_{NDM-1} gene that confers resistance to carbapenems)
  - *Escherichia coli* with plasmid-mediated *mcr-1* gene that confers resistance to colistin (originally described in China)

Marston HD, et al. *JAMA*. 2016;316:1193-1204.

Antibiotic Resistance Threats in the United States, 2013

Gram-Negative Organism	Cases (%)	Deaths (%)	Threat Level
ESBL-producing Enterobacteriaceae	26,000 (1.93)	1700 (7.44)	Serious
Multidrug-resistant *Pseudomonas aeruginosa*	6700 (0.5)	440 (1.92)	Serious
Carbapenem-resistant Enterobacteriaceae	9300 (0.69)	610 (2.67)	Urgent
Multidrug-resistant *Acinetobacter* spp.	7300 (0.54)	500 (2.18)	Serious

Estimated annual incidence of infection due to notable antimicrobial-resistant organisms
Total: 1,349,766 cases and 22,840 deaths
ESBL, extended-spectrum beta-lactamase

Thabit AK, et al. *Expert Opin Pharmacother*. 2015;16:159-177.
Available at: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.

WHO Priority Pathogen List for R&D of New Antibiotics

- **Priority 1: Critical**
  - Enterobacteriaceae, carbapenem-resistant, ESBL-producing
  - *Pseudomonas aeruginosa*, carbapenem-resistant
  - *Acinetobacter baumannii*, carbapenem-resistant
- Includes multidrug-resistant bacteria that pose a particular threat in hospitals, nursing homes, and among patients whose care requires devices such as ventilators and blood catheters
- Can cause severe and often deadly infections such as bloodstream infections and pneumonia
- Resistant to a large number of antibiotics, including the best available antibiotics for treating multidrug-resistant bacteria

Released February 27, 2017
WHO. Available at: http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/.

Bloodstream Infections Caused by MDR Gram-Negative Bacteria

- 891 patients with monomicrobial MDR BSI at Duke University
  - 292 patients (33%) had BSI due to MDR pathogens and more likely to have:
    - History of transplant (19% versus 13%; *P* = 0.02)
    - Prior Gram-negative infection (46% versus 33%; *P* = 0.0003)
    - Hospital-acquired infection (35% versus 28%; *P* = 0.05)
- Most commonly isolated Gram-negative bacteria were:
  - *Escherichia coli* (37%; 330/891)
  - *Klebsiella pneumoniae* (19%; 166/891)
  - *Pseudomonas aeruginosa* (13%; 119/891)
- MDR phenotype was most common in *Escherichia coli* (50%) and *Citrobacter freundii* (44%)

MDR, multidrug-resistant (nonsusceptible to at least one agent in greater than or equal to 3 antimicrobial categories); BSI, bloodstream infections

Thaden JT, et al. *Antimicrob Agents Chemother.* 2017;61:e01709-16.

Ceftolozane-Tazobactam

- Antipseudomonal cephalosporin plus beta-lactamase inhibitor
- Spectrum of activity: Gram-negatives, including MDR *Pseudomonas aeruginosa* and ESBL-producing strains
- FDA approval in December 2014
  - Complicated Urinary Tract Infections (cUTI), including pyelonephritis
  - Complicated Intraabdominal Infections (cIAI) *plus* metronidazole
  - IV dose: 1.5 g (1 g ceftolozane; 0.5 g tazobactam) q8h (1-h infusion)
- Dosage adjustment in patients with renal impairment (CrCl ≤50 mL/min) or ESRD on hemodialysis
- Most common adverse reactions (≥5% in either indication) are nausea, diarrhea, headache, and pyrexia

Scott LJ. *Drugs.* 2016;76:231-242.
Zhanel GG, et al. *Drugs.* 2014;74:31-51.
Liscio JL, et al. *Int J Antimicrob Agents.* 2015;46:266-271.

Ceftolozane-Tazobactam

- Demonstrated potent *in vitro* activity against *Pseudomonas aeruginosa* isolates tested that had:
  - Chromosomal AmpC *or*
  - Loss of outer membrane porin (OprD) *or*
  - Up-regulation of efflux pumps (MexXY, MexAB)
- Not active against bacteria producing metallo-β-lactamases
- Current FDA susceptibility interpretive criteria:

	Minimum Inhibitory Concentrations (mg/L)		
Pathogen	Susceptible (S)	Intermediate (I)	Resistant (R)
Pseudomonas aeruginosa	≤4 / 4*	8 / 4*	≥16 / 4*

* Ceftolozane-tazobactam susceptibility testing performed with a fixed 4 µg/mL concentration of tazobactam

ZERBAXA® (ceftolozane and tazobactam) for injection, for intravenous use Prescribing Information. Merck & Co., Inc., Whitehouse Station, NJ. October 2016.
Takeda S, et al. *Int J Antimicrob Agents.* 2007;30:443-5.
Takeda S, et al. *Antimicrob Agents Chemother.* 2007;51:826-30.
Castanheira M, et al. *Antimicrob Agents Chemother.* 2014;58:6844-50.

Ceftolozane-Tazobactam
Current Availability of Susceptibility Tests

- Disks
  - MAST Disk: Hardy Diagnostics, commercially-available FDA-approved diameters:
    - Enterobacteriaceae: >21mm (S), 18-20mm (I), and <17mm (R)
    - *P. aeruginosa*: >21mm (S), 17-20mm (I), and <16mm (R)
- Gradient Strips
  - Breakpoints published in the package insert and latest CLSI M100 document
    - Etest (Biomérieux) can be ordered from http://www.biomerieux-diagnostics.com/etest-ceftolozane-tazobactam-c-t-256 (FDA clearance pending)
    - MIC test strip (Liofilchem) C/T test strips can be ordered directly from Liofilchem (http://www.liofilchem.net/en/pdf/mic_brochure.pdf). Approved in USA, Europe, Canada
- Panels
  - Vitek 2 (Biomérieux) card approved and will undergo beta-testing; not yet commercially available, software updates started in March 2017
  - Microscan (Beckman Coulter) expect commercial availability in late 2017/2018
  - Phoenix (BD) expect commercial availability late 2017/2018
  - Trek Panel (ThermoFisher Scientific) commercially available since Q1 2016

Ceftazidime-Avibactam

- Antipseudomonal cephalosporin plus beta-lactamase inhibitor
- Spectrum of activity: Gram-negatives, including MDR *Pseudomonas aeruginosa*, ESBL-producing strains, and KPCs
- FDA approval in February 2015 (originally based on Phase 2 data)
  - Complicated Urinary Tract Infections (cUTI), including pyelonephritis
  - Complicated Intraabdominal Infections (cIAI) *plus* metronidazole
  - IV dose: 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)
- Dosage adjustment in patients with CrCl ≤50 mL/min
- Most common adverse reactions in cIAI (≥5%) patients are diarrhea, nausea, and vomiting. The most common (3%) in cUTI patients are diarrhea and nausea

Zhanel GG, et al. *Drugs.* 2013;73:159-177.
Liscio JL, et al. *Int J Antimicrob Agents.* 2015;46:266-271.

Ceftazidime-Avibactam

- Demonstrated *in vitro* activity against *Pseudomonas aeruginosa* in the presence of:
  - some AmpC beta-lactamases *or*
  - certain strains lacking outer membrane porin (OprD)
- Not active against bacteria producing metallo-β-lactamases and may not have activity against Gram-negative bacteria that overexpress efflux pumps or have porin mutations
- Current FDA susceptibility interpretive criteria:

	Minimum Inhibitory Concentrations (mg/L)	
Pathogens	Susceptible (S)	Resistant (R)
Pseudomonas aeruginosa Enterobacteriaceae	≤8 / 4*	≥16 / 4*

*Ceftazidime/avibactam susceptibility testing performed with a fixed 4 µg/mL concentration of avibactam

AVYCAZ® (ceftazidime and avibactam) for injection, for intravenous use. Prescribing Information, Allergan USA, Inc., Irvine, CA. January 2017.

Ceftazidime-Avibactam
Current Availability of Susceptibility Tests

- **Approved Tests**
  - KB Disks from Hardy Diagnostics and BD
  - Custom Sensititre (ThemoFisher)
- **Tests in Development**
  - Etest (Biomérieux) can be ordered from http://www.biomerieux-diagnostics.com/etest-ceftazidime-avibactam-cza-256 (FDA clearance pending)
  - MIC test strip (Liofilchem) can be ordered directly from Liofilchem (http://www.liofilchem.net/en/pdf/mic_brochure.pdf). (Not cleared by FDA)
- **Automated Tests**
  - Vitek 2: Software validation Q1 2017, expected approval Q2 2018
  - Microscan (Beckman Coulter): expect commercial availability in mid 2018
  - Phoenix (BD): FDA-approved, but not available yet

Decreased Clinical Cure Rates in cIAI
Patients with Baseline CrCl of 30 to ≤50 mL/min

Ceftolozane-Tazobactam (Zerbaxa®) - Product Package Insert

Renal Function	Ceftolozane-Tazobactam plus Metronidazole	Meropenem
Normal / Mild Impairment (CrCl: >50 mL/min)	85% (312/366)	88% (355/404)
Moderate Impairment (CrCl: 30 to ≤50 mL/min)	48% (11/23)	69% (9/13)

Ceftazidime-Avibactam (Avycaz®) - Product Package Insert

Renal Function	Ceftazidime-Avibactam plus Metronidazole	Meropenem
Normal / Mild Impairment (CrCl: >50 mL/min)	85% (322/379)	86% (321/373)
Moderate Impairment (CrCl: 30 to ≤50 mL/min)	45% (14/31)	74% (26/35)

Warning and Precautions

- **Ceftolozane-Tazobactam (Zerbaxa® – Product Package Insert)**
  - *In a subgroup analysis of a Phase 3 complicated intraabdominal infection (cIAI) trial, clinical cure rates were lower in patients with baseline creatinine clearance (CrCl) of 30 to ≤50 mL/min. The reduction in clinical cure rates was more marked in the ZERBAXA plus metronidazole arm compared to the meropenem arm. A similar trend was also seen in the cUTI trial. Monitor CrCl at least daily in patients with changing renal function and adjust the dosage of ZERBAXA accordingly (see Dosage and Administration)*

Estimated CrCl (mL/min)	Recommended Dosage Regimen for ZERBAXA (ceftolozane and tazobactam)
30 to 50	ZERBAXA 750 mg (500 mg and 250 mg) IV q8h
15 to 29	ZERBAXA 375 mg (250 mg and 125 mg) IV q8h
End-stage renal disease (ESRD) on hemodialysis (HD)	A single loading dose of ZERBAXA 750 mg (500 mg and 250 mg) followed by a ZERBAXA 150 mg (100 mg and 50 mg) maintenance dose IV q8h

ZERBAXA® (ceftolozane and tazobactam) Prescribing Information. Merck & Co., Inc. Whitehouse Station, NJ. October 2016.

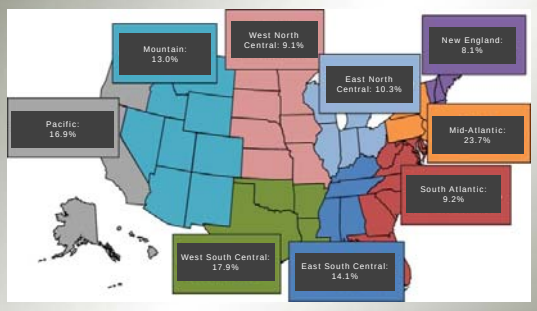
Warning and Precautions

- **Ceftazidime-Avibactam (Avycaz® – Product Package Insert)**
  - *In a Phase 3 complicated intraabdominal infection (cIAI) trial, clinical cure rates were lower in a subgroup of patients with baseline creatinine clearance (CrCl) of 30 to ≤50 mL/min compared to those with CrCl >50 mL/min. The reduction in clinical cure rates was more marked in the AVYCAZ plus metronidazole arm compared to the meropenem arm. Within this subgroup, patients treated with AVYCAZ received 33% lower daily dose than is currently recommended for patients with CrCl 30 to ≤50 mL/min. Monitor CrCl at least daily in patients with changing renal function and adjust the dosage of AVYCAZ accordingly (see Dosage and Administration)*

Estimated CrCl (mL/min)	Recommended Dosage Regimen for AVYCAZ (ceftazidime and avibactam)
31 to 50	AVYCAZ 1.25 grams (1 gram and 0.25 grams) IV q 8h
16 to 30	AVYCAZ 0.94 grams (0.75 grams and 0.19 grams) IV q 12h
6 to 15	AVYCAZ 0.94 grams (0.75 grams and 0.19 grams) IV q 24h
≤5	AVYCAZ 0.94 grams (0.75 grams and 0.19 grams) IV q 48h

AVYCAZ® (ceftazidime and avibactam) for injection, for intravenous use. Prescribing Information, Allergan USA, Inc., Irvine, CA. January 2017.

ESBL Phenotype Among Enterobacteriaceae
Isolates in United States Hospitals – 2014



Castanheira M, et al. *Antimicrob Agents Chemother.* 2016;60:4770-7.

Use of Non-carbapenem Beta-Lactams for the Treatment of ESBL Infections

- **Cefepime**
  - Do not favor use for serious ESBL infections
  - Non-severe ESBL-producing infections (e.g., UTIs with cefepime MICs ≤2 mg/L) so pharmacodynamic targets are met
  - Non-severe ESBL-producing infections with MICs of 4–8 mg/L, recommend 2 g q8h, possibility as a continuous infusion
- **Piperacillin-Tazobactam**
  - Reasonable options for low- to moderate-severity infections resulting from urinary or biliary sources, and infections with piperacillin MIC <4 mg/L
  - Carbapenem may be more appropriate first in critically ill patients, patients with high inoculum infections, and elevated piperacillin MIC values
  - Regardless, recommend administering 4.5 g q6h (or 4.5 g q8h as extended infusion) for patients with invasive ESBL infections

Tamma PD, Rodriguez-Bano J. *Clin Infect Dis.* 2017;64:972-80.

Use of Newer Beta-Lactam/Beta-Lactamase Inhibitors for the Treatment of ESBL Infections

Ceftolozane-Tazobactam

- Ceftolozane has good activity against Enterobacteriaceae, but limited activity against ESBLs
- Tazobactam is a potent, irreversible inhibitor of most ESBLs
- MIC_{50} / MIC_{90} for ESBL-producing strains of:
  Escherichia coli: 0.5 / 4 mg/L
  Klebsiella pneumoniae: 4 / >32 mg/L
- Evidence suggests a potential role, however more clinical data are needed and significant expense is a limiting factor

Tamma PD, Rodriguez-Bano J. *Clin Infect Dis.* 2017;64:972-80.

- Efficacy of ceftolozane-tazobactam (C-T), pooled analysis Phase 3 cUTI & cIAI trials
- 150 patients (11%) had ESBL-producing Enterobacteriaceae (pooled ME population)
- MIC_{50} / MIC_{90} for 159 ESBL-producing strains:
  Ceftolozane-Tazobactam: 0.5 / 8 mg/L (81.8% S)
  Piperacillin-Tazobactam: 8 / 128 mg/L (73.0% S)
  Cefepime: 32 / 64 mg/L (19.6% S)
- Clinical cure rates for ME patients:
  98.0% (49/50) ESBL – *Escherichia coli* for C-T
  94.4% (17/18) ESBL – *K. pneumoniae* for C-T
  82.6% (38/46) for levofloxacin
  88.5% (23/26) for meropenem

Popejoy MW, et al. *J Antimicrob Chemother.* 2017;72:268-272.

Use of Newer Beta-Lactam/Beta-Lactamase Inhibitors for the Treatment of ESBL Infections

Ceftazidime-Avibactam

- Tends to be more active *in vitro* against ESBL-producers than ceftolozane-tazobactam
- MIC_{50} / MIC_{90} for ESBL-producing strains of:
  Escherichia coli: 0.12 / 0.25 mg/L
  Klebsiella pneumoniae: 0.5 / 1 mg/L
- Showed similar microbiological response as doripenem against ceftazidime-resistant Enterobacteriaceae, most being ESBL-producing in cUTI study
- Evidence suggests a potential role, however more clinical data are needed and significant expense is a limiting factor

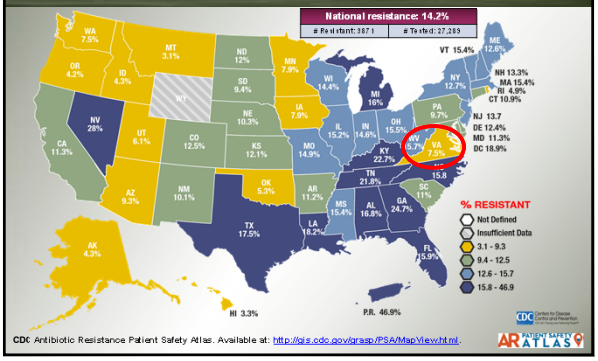
Tamma PD, Rodriguez-Bano J. *Clin Infect Dis.* 2017;64:972-980.

- Efficacy of ceftazidime-avibactam (Cef-Avi) among mMITT population Phase 3 cIAI trials
- 124 patients had Enterobacteriaceae after testing MIC screen positive (ceftriaxone and/or ceftazidime MIC >2 mg/L)
- Clinical cure rates for mMITT patients:
  87.5% (49/56) MIC-screen positive for Cef-Avi
  86.5% (64/74) MIC-screen positive for Meropenem
  92.5% (37/40) ESBL - ENT for Cef-Avi
  84.9% (45/53) ESBL - ENT for Meropenem
  81.6% (337/413) all patients for Cef-Avi
  85.1% (349/410) all patients for Meropenem

ENT, Enterobacteriaceae

Mendes RE, et al. *Antimicrob Agents Chemother* 2017;61(6). pii: e02447-16.

Multidrug-Resistant *Pseudomonas aeruginosa*
Isolates in United States Hospitals: 2011–2014



CDC Antibiotic Resistance Patient Safety Atlas. Available at: http://gis.cdc.gov/grasp/PSA/MapView.html.

Ceftolozane-Tazobactam

Ceftolozane-tazobactam susceptibility patterns of 3851 *Pseudomonas aeruginosa* isolates from United States hospitals (PACTS, 2012–2015):

	% Susceptible	MIC_{50}	MIC_{90}
All isolates (n=3851)	97.0	0.5	2
Meropenem - Nonsusceptible (n=699)	87.6	1	8
Multidrug-resistant (MDR) (n=607)	84.0	2	8
Extensively drug-resistant (XDR) (n=363)	76.9	2	16
Nonsusceptible to cefepime, ceftazidime, meropenem, and piperacillin-tazobactam (n=241)	68.0	4	>32

Shortridge D, et al. *Antimicrob Agents Chemother* 2017;61(7): pii: e00465-17.

Ceftolozane-Tazobactam

- Isolates displaying derepressed AmpC had ceftolozane-tazobactam MIC values ranging from 1 to 16 mg/L[1]
- The development of high-level resistance to ceftolozane-tazobactam appears to occur efficiently only in a *Pseudomonas aeruginosa* mutator background, in which multiple mutations lead to overexpression and structural modifications of AmpC[2]
- *Pseudomonas aeruginosa* is able to adapt to efficacious beta-lactams, including newer cephalosporin ceftolozane, through a variety of mutations affecting its intrinsic beta-lactamase, AmpC[3]

[1] Castanheira M, et al. *Antimicrob Agents Chemother.* 2014;58:6844-55.
[2] Cabot G, et al. *Antimicrob Agents Chemother.* 2014;58:3091-9.
[3] Berrazeg M, et al. *Antimicrob Agents Chemother.* 2015;59:6248-55.

"Real World" Treatment Reports
Ceftolozane-Tazobactam for MDR *Pseudomonas aeruginosa*

- 15 patients with XDR infections: Clinical cure 67%; All-cause in-hospital mortality 27%; 6/8 microbiological cure; 2 microbiological failures; combination therapy in 10 of 15: 4 failures at end of therapy[1]
- Multicenter, retrospective study of 35 patients infected with carbapenem-resistant *P. aeruginosa*; pneumonia most common indication (n=18); treatment success rate was 74% (n=26); treatment failure in all cases where MIC ≥8 mg/L[2]
- Multicenter, retrospective study of 12 patients; salvage therapy for severe MDR infections (83% presented as septic shock; 3 deaths); pneumonia in 6 patients (50%); microbiological eradication in 10 patients (83.3%); however 2 patients had late reoccurrence with C-T resistant MDR-PA[3]

[1] Dinh A, et al. *Int J Animicrob Agents.* 2017;49:782-3.
[2] Munita JM, et al. *Clin Infect Dis.* 2017;65:158-61.
[3] Caston JJ, et al. *Antimicrob Agents Chemother.* 2017;61:e02136-16.

Ceftolozane-Tazobactam

- Ongoing Phase 3 Trial: Ventilated nosocomial pneumonia (NCT02070757)
  - *Increased dose*: 3.0 g (2 g ceftolozane; 1 g tazobactam) q8h
  - Treatment duration of 8 days; exception being 14 days for *Pseudomonas aeruginosa*
- Initial report on treating respiratory infections caused by MDR *Pseudomonas aeruginosa:*

Age; Sex	Prior Antibiotics	Clinical / Microbiologic Outcomes	Susceptibilities (MIC, µg/mL)
69 y; male	Ciprofloxacin	Cure / Eradication	Ceftolozane-Tazobactam (0.25) Meropenem (>8) Cefepime (8) Piperacillin-Tazobactam (<16) Ciprofloxacin (>2) Tobramycin (<2)
63 y; male	Meropenem, Ciprofloxacin	Cure / Eradication	Ceftolozane-Tazobactam (1) Meropenem (>8) Cefepime (>16) Colistin (susceptible) Ciprofloxacin (>2) Tobramycin (>8) Polymyxin (susceptible) Piperacillin-Tazobactam (>64)
52 y; male	Meropenem, Linezolid	Cure / Eradication	Ceftolozane-Tazobactam (1) Meropenem (>8) Cefepime (16) Tobramycin (<2) Piperacillin-Tazobactam (>16) Ciprofloxacin (<0.5)

Zhanel GG, et al. *Drugs.* 2014;74:31-51.
Gelfand MS, Cleveland KO. *Clin Infect Dis.* 2015;61:853-855 [letter to editor].

Ceftazidime-Avibactam

Ceftazidime-avibactam activity tested against *Pseudomonas aeruginosa* isolates

	Cumulative (%) inhibited at MIC in mg/L of:			MIC_{50} / MIC_{90} (mg/L)
	4	8	16	
All isolates (n=7452)	91.4	97.0	98.8	2 / 4
Ceftazidime – Nonsusceptible (n=1168)	59.9	81.0	92.2	4 / 16
Meropenem – Nonsusceptible (n=1341)	65.5	86.2	94.0	4 / 16
Piperacillin-tazobactam – Nonsusceptible (n=1449)	62.0	85.4	94.1	4 / 16
Levofloxacin – Nonsusceptible (n=1868)	75.1	90.4	95.8	4 / 8
Gentamicin – Nonsusceptible (n=873)	73.9	87.6	92.9	2 / 16
Amikacin – Nonsusceptible (n=224)	69.2	79.5	87.1	4 / 32
Colistin – Nonsusceptible (n=45)	86.7	88.9	95.6	2 / 16
Multidrug-resistant (MDR) (n=1151)	57.3	82.1	92.5	4 / 16
Extensively drug-resistant (XDR) (n=698)	46.0	75.8	92.4	8 / 32
Nonsusceptible to Meropenem, Ceftazidime, and Piperacillin-tazobactam (n=607)	42.5	71.2	88.4	8 / 32

Sader HS, et al. *Antimicrob Agents Chemother.* 2017;61:e02252-16.

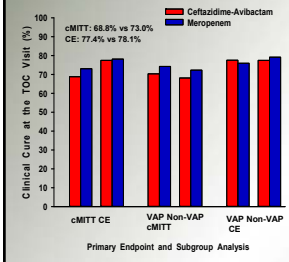
Resistance to Ceftazidime-Avibactam

- β-lactam-resistant *Pseudomonas aeruginosa* clinical isolates
  - 18.5% of archived isolates (n=54) from a decade ago were resistant to ceftazidime-avibactam with MIC of ≥16 µg/mL
- Acquired resistance, which may be driven by altered outer membrane permeability or overexpressed efflux pumps
- Combination poses a potential advantage
  - Addition of colistin reduced resistance to 7% of strains
  - Addition of fosfomycin reduced resistance to 1.9% of strains
- Resistance was not due to changes in penicillin-binding-protein (PBP) sequence or changes to β-lactamase sequence or expression level

Winkler ML, et al. *Antimicrob Agents Chemother.* 2015;59:1020-9.

Nosocomial Pneumonia Including VAP

Phase 3, Randomized, Multicenter Study (REPROVE Study)



Secondary Efficacy Endpoints

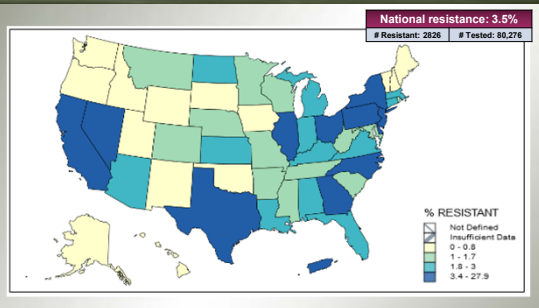
Per Pathogen Favorable Microbiological Response at TOC	Ceftazidime-Avibactam	Meropenem
mMITT		
K. pneumoniae	62.7% (37/59)	74.6% (53/71)
P. aeruginosa	37.9% (22/58)	38.3% (18/47)
eME		
K. pneumoniae	78.4% (29/37)	79.6% (39/49)
P. aeruginosa	42.9% (18/42)	40.0% (14/35)

TOC, test-of-cure ; cMITT, clinically-modified intent-to-treat; CE, clinically evaluable; mMITT, microbiological MITT; eME, extended microbiological evaluable

Presented at 27th ECCMID, Vienna, Austria 2017; Abstract OS0603
Results Reported: ClinicalTrials.gov: NCT01808092

Carbapenem-Resistant Enterobacteriaceae

Isolates in United States Hospitals: 2011–2014



CDC Antibiotic Resistance Patient Safety Atlas. Available at: http://gis.cdc.gov/grasp/PSA/MapView.html.

"Real World" Treatment Reports

Ceftazidime-Avibactam for Resistant Gram-Negative Infections

- REPRISE Study [1]
  - Ceftazidime-avibactam or best-available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* cUTI or cIAI
- Case Series from Compassionate-use [2]
  - Carbapenem-resistant Enterobacteriaceae or *Pseudomonas aeruginosa*
- Ceftazidime-avibactam was superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia [3]
  - Higher rates of clinical success (*P*=0.006) and survival (*P*=0.01) and less nephrotoxicity than aminoglycoside- and colistin-containing regimens
- Ceftazidime-avibactam had a 23% reduced risk for death compared to colistin for carbapenem-resistant Enterobacteriaceae [4]
  - Ceftazidime-avibactam also had 64% probability of a better outcome

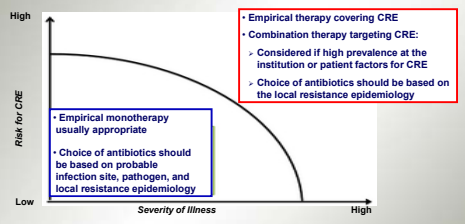
1. Carmeli Y, et al. *Lancet Infect Dis.* 2016;16:661-673.
2. Temkin E, et al. *Antimicrob Agents Chemother.* 2017;61:e01964-16.
3. Shields RK, et al. *Antimicrob Agents Chemother.* 2017;61:e00883-17.
4. van Duin D, et al. *Clin Infect Dis.* 2017;65: doi:10.1093/cid/cix783.

Ceftazidime-Avibactam
Emergence of Resistance among Enterobacteriaceae

- First clinical case of a ceftazidime-avibactam-resistant *Klebsiella pneumoniae*, in a patient with no previous exposure[1]
  - Resistance due to porin mutations and the increased expression of KPC-3[2]
- 37 CRE-infected patients treated with ceftazidime-avibactam[3]
  - Clinical success was 59% (22/37) and 30-day survival was 76% (28/37)
  - CRE infections recurred within 90 days in 23% (5/22)
  - Resistance detected in 30% (3/10) of microbiologic failures
  - Development of resistance conferring bla_{KPC-3} mutations in *K. pneumoniae* within 10 to 19 days of ceftazidime-avibactam exposure, but may be ameliorated if carbapenem susceptibility is restored [4]
- Surveillance studies continue to document low frequency of ceftazidime-avibactam resistance among Enterobacteriaceae isolates carrying bla_{KPC}[5,6]

1. Humphries RM, et al. *AAC.* 2015;59:6605-7.
2. Humphries RM, et al. *AAC.* 2017;61:doi:10.1128/AAC.00537-17.
3. Shields RK, et al. *Clin Infect Dis.* 2016;63:1615-8.
4. Shields RK, et al. *AAC.* 2017;61:e02097-16.
5. Castanheira M, et al. *AAC.* 2017;61:e02369-16.
6. Spellberg B, Bonomo RA. *Clin Infect Dis.* 2016;63:1619-21.

Monotherapy vs Combination Therapy
Carbapenem-Resistant Enterobacteriaceae (CRE) Infections



Tangden T, Giske CG. *J Intern Med.* 2015;277:501-12.

Meropenem-Vaborbactam

- Carbapenem plus beta-lactamase inhibitor
- Spectrum of activity: Gram-positives and Gram-negatives (is stable to hydrolysis by most beta-lactamases, including penicillinases and cephalosporinases) and vaborbactam protects meropenem from degradation by certain serine beta-lactamases (i.e., KPCs)
- FDA approval in August 2017
  - Complicated Urinary Tract Infections (cUTI), including Pyelonephritis
  - IV dose: 4 g (2 g meropenem; 2 g vaborbactam) q8h (3-h infusion)
- Dosage adjustment in patients with an estimated glomerular filtration rate (eGFR <50 mL/min/1.73m^2) or ESRD on hemodialysis
- Most common adverse reactions (≥3%) were headache, phlebitis/infusion site reactions, and diarrhea

Vabomere™ (meropenem and vaborbactam) Prescribing Information. The Medicines Company, Parsippany, NJ. August 2017.

Complicated Urinary Tract Infections, including Acute Pyelonephritis

m-MITT Population	EOIVT		Eradication Rate at TOC	
	Ceftolozane-Tazobactam	Levofloxacin	Ceftolozane-Tazobactam	Levofloxacin
Composite Cure Rates (n=800)			76.9%	68.4%
No Levofloxacin Resistance (n=212)			82.6%	79.7%
Levofloxacin Resistance (n=588)			60.0%	39.3%
	Ceftazidime-Avibactam	Doripenem	Ceftazidime-Avibactam	Doripenem
Composite Cure Rates (n=810)	70.2%[a]	66.2%[a]	71.2%	64.5%
	Meropenem-Vaborbactam	Piperacillin-Tazobactam	Meropenem-Vaborbactam	Piperacillin-Tazobactam
Composite Cure Rates (n=366)	98.4%	94.3%	76.5%	73.2%

m-MITT, Microbiological modified intent-to-treat
EOIVT, Overall success at end of IV treatment
TOC, Test of cure
a, Symptomatic response at Day 5

Zerbaxa® Prescribing Information, October 2016.
Ayvcaz® Prescribing Information, January 2017.
Vabomere™ Prescribing Information, August 2017.

Meropenem-Vaborbactam

- *Efficacy, Safety, Tolerability of Carbavance Compared to Best Available Therapy in Serious Infections Due to Carbapenem-Resistant Enterobacteriaceae in Adults (TANGO-2)* (NCT02168946; clinicaltrials.gov)
- Data Safety and Monitoring Board's recommendation to discontinue randomization into the TANGO-2 trial was based on the results of an interim analysis of data
  - *Efficacy:* Statistically-significant differences favor meropenem-vaborbactam over best available therapy for clinical cure at the test of cure visit in the protocol-specified primary population (all patients with microbiologically-evaluable CRE)
  - *Mortality rates:* Lower among patients treated with meropenem-vaborbactam
  - *Renal toxicity:* Lower rates of renal adverse events and serum creatinine increases among patients treated with meropenem-vaborbactam than best available therapy – particularly among patients receiving colistin and aminoglycosides

Press Release, July 25, 2007 – The Medicines Company

Antibiotic Treatment of Multidrug-Resistant Gram-Negative Organisms

- Multidrug-resistant Gram-negative bacteria have become widespread and increasing worldwide
- New agents for treatment of Gram-negative infections are promising and could help preserve and enhance our antibiotic armamentarium
- Choice of empiric therapy has become more difficult for serious infections because of antimicrobial resistance to first-line agents
- Clinicians also have the dilemma between choosing:
  - an agent that is inactive versus a broad-spectrum agent
  - monotherapy versus combination therapy
  - determining the role of adjunctive therapy