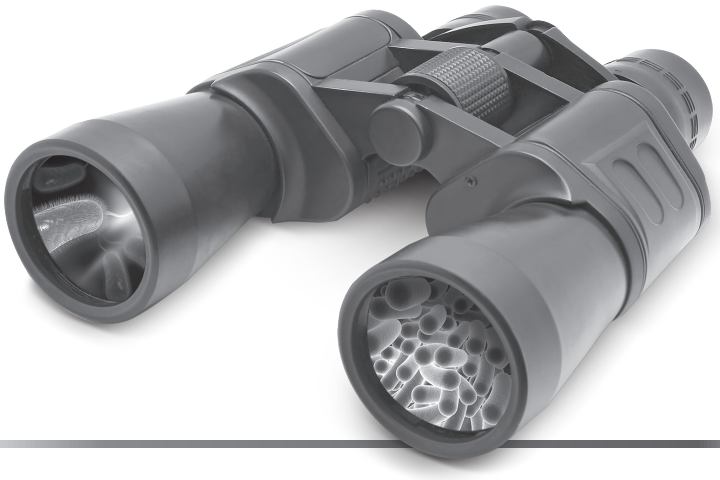

Novel Approaches in the Management of *C. difficile* Infection

Stuart Johnson, MD

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Chicago, IL

Overview

- Pathogenesis of CDI* and risk for infection
- Current guideline recommendations for CDI treatment
- Alternative approaches to therapy for recurrent CDI
- Emerging approaches in treating CDI

*CDI, *Clostridium difficile* infection

Case History

66-year-old woman with multiple medical problems:

- Developed CDI with diarrhea 5 days after finishing a course of clindamycin for a dental infection; she responded to treatment with metronidazole (500 mg TID x 14 d), but
- Developed recurrent CDI with diarrhea & severe abdominal cramping 3 days after stopping metronidazole (WBC 16,000/mm^3, serum creatinine 2.5 mg/dL); she responded to treatment with oral vancomycin (125 mg QID x 10 d), but
- Developed recurrent CDI with diarrhea 10 days after stopping vancomycin; she responded to vancomycin treatment followed by a vancomycin taper, but
- Developed recurrent CDI with diarrhea 7 days after finishing the vancomycin taper

What Would You Recommend Now?

1. Fecal microbiota transplant
2. Repeat vancomycin treatment followed by taper/pulse
3. Vancomycin 125 mg QID × 10 d followed by rifaximin 400 mg BID × 14 d
4. Fidaxomicin 200 mg BID × 10 d
5. Fidaxomicin 200 mg BID × 10 d followed by fidaxomicin 200 mg QD × 7 d, then once every other day for 2–3 weeks

Pathogenesis of *C. difficile* Infection

Antibiotic therapy

↓

Disturbed colonic microflora ⇐ "Dysbiosis"

(loss of colonization resistance)

↓

Colonization by *C. difficile* ⇐ Exposure

↓

Anti-toxin immunity

Toxin A & Toxin B ⇐ Toxin effects

↙ ↘

Symptomless carriage Diarrhea & colitis

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40. Kyne L, et al. *Lancet.* 2001;357:189-93.

Pathogenesis of *C. difficile* Infection

Antibiotic therapy

↓

Disturbed colonic microflora ⇐ "Dysbiosis"

(loss of colonization resistance)

- Antimicrobials
- Chemotherapy
- Neonatal state
- Enteric infection
- IBD with colitis

↓

Colonization by *C. difficile*

↓

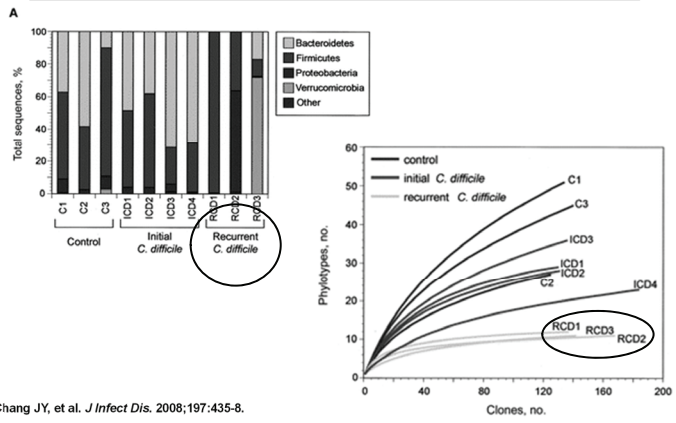
Toxin A & Toxin B

↙ ↘

Symptomless carriage Diarrhea & colitis

Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.

Decreased Diversity of Fecal Microbiome in CDI



Chang JY, et al. *J Infect Dis.* 2008;197:435-8.

Pathogenesis of *C. difficile* Infection

Antibiotic therapy

↓

Disturbed colonic microflora

(loss of colonization resistance)

↓

Colonization by *C. difficile*

↓

Toxin A & Toxin B

↙ ↘

Symptomless carriage **Diarrhea & colitis**

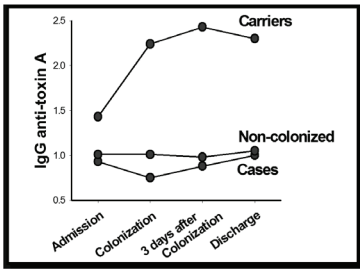
Anti-toxin Immunity ⇐

Anti-Toxin A Antibodies
Anti-Toxin B Antibodies ?
Antibodies against
non-toxin antigens ?

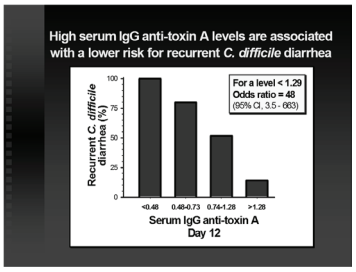
Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.

Anti-toxin Immunity Protects Against CDI

- High serum anti-toxin in symptomless carriers



- Serum anti-toxin response & protection against recurrent CDI

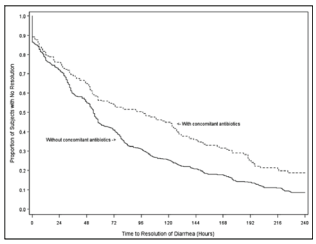


Kyne L, et al. *N Engl J Med.* 2000;342:390-397.
Kyne L, et al. *Lancet.* 2001;357:189-193.

C. difficile Infection: Basic Principles of Management

- Suspect on clinical grounds
- **Discontinue non-essential antibiotics**
- Confirm presence of toxin-producing *C. difficile* by stool testing (usually PCR or EIA)
- Empiric treatment best avoided UNLESS:
  - Very high clinical index of suspicion
  - OR very severe illness

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

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

CA = concomitant antibiotics

Treatment Guidelines for CDI in Adults: SHEA/IDSA 2010

- Metronidazole is the drug of choice for the initial episode of mild-moderate CDI (500 mg orally TID) for 10–14 days. (A-I)
- Vancomycin is the drug of choice for an initial episode of severe CDI. The dose is 125 mg orally QID for 10–14 days. (B-I)
- Vancomycin orally (and per rectum if ileus is present) with or without metronidazole IV ... for severe, complicated CDI. Vancomycin is dosed at 500 mg. (C-III)
- Consider colectomy in severely ill patients…(ideally before) serum lactate rises to 5 mmol/L and WBC 50,000 per mL. (B-II)

Cohen SH, et al. *Infect Cont Hosp Epidemiol.* 2010;31:431-55.

Randomized Trials Supporting Vancomycin (VAN) Over Metronidazole (MTR) for Treatment of Severe CDI

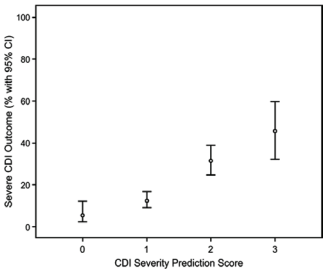
	Overall cure	Cure "Severe"	
• ***Zar FA, et al. Clin Infect Dis. 2007;45:302-7*:**			
All Patients	135/150 (90)	59/69 (86)	
VAN	69/71 (97)	30/31 (97)	] *p =0.02*
MTR	66/79 (84)	29/38 (76)	
• ***Louie T, et al. ICAAC, Chicago 2007 (Abstract K-425a)*:**			
Tolevamer	124/266 (47)	35/95 (37)	
VAN	109/134 (81)	28/33 (85)	] *p =0.04*
MTR	103/143 (72)	37/57 (65)	

Clinical Prediction Rule for Severe CDI

Derivation & validation from a cohort of 638 patients at 3 Centers

1 point for each:
- -age ≥65 years
- -peak creatinine ≥2 mg/dL
- -peak WBC ≥20k cells/μL

Severe CDI:
- -colectomy
- -admission to ICU or
- -death from CDI or with CDI as a contributor



Current IDSA/SHEA guidelines definition of severity:
WBC >15,000/mm^3 or,
Cr >1.5 x baseline

Na X, et al. *PLoS One.* 2015;10(4):e0123405.

Colectomy vs. Temporary Loop Ileostomy in Severe Complicated or Fulminant CDI

- Subtotal colectomy can be life-saving in severe complicated CDI, but should be performed before lactate reaches 5 mg/dL or WBC is >50,000/mm^3 to avoid mortality which is high even with colectomy.
- Diverting loop ileostomy followed by intraoperative lavage of 8 L of warmed polyethylene glycol and 500 mg vancomycin q8h was performed in 42 patients (35 laparoscopically) and compared to the previous 42 historical colectomy patients.
  - Mortality was19% vs 50%; odds ratio, 0.24; p=0.006.
  - Preservation of the colon was achieved in 39 of 42 patients (93%).

Neal MD, et al. *Ann Surg.* 2011;254:423-7.

Treatment Guidelines for CDI in Adults: SHEA/IDSA 2010 – *Recurrent CDI*

- Treatment of the first recurrence is usually with the same regimen as for the initial episode (A-II) but should be stratified by disease severity (C-III)
- Do not use metronidazole beyond first recurrence or for long-term chronic therapy (B-II)
- Treatment of the second or later recurrence with vancomycin using a taper and/or pulse regimen is the preferred next strategy (B-III)
- No recommendations can be made regarding prevention of recurrent CDI in patients requiring continued antimicrobial therapy (C-III)

Cohen SH, et al. *Infect Cont Hosp Epidemiol.* 2010;31:431-55.

New Data on CDI Treatment Since Publication of the IDSA/SHEA Guidelines

- Fidaxomicin phase 3 trials, including a randomized sub-study of patients with first CDI recurrence
- Randomized trial of FMT
- Findings from the largest and most rigorous randomized comparison of metronidazole and vancomycin (phase 3 trials of tolevamer)

FMT, fecal microbiota transplantation

Phase 3 Trials of Tolevamer for CDI

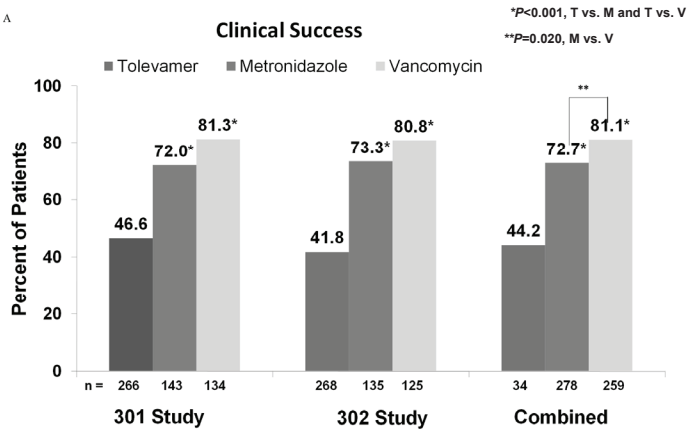
Comparison of a non-antibiotic, toxin-binder to treatment with vancomycin and metronidazole

- 1118 patients randomized between 2005 & 2007
  - Study 301, n=574 (91 sites in the US & Canada)
  - Study 302, n=544 (109 sites in Europe, Australia, & Canada)
  - 1071 included in the full analysis set (FAS)*
    - tolevamer, n=534
    - metronidazole, n=278
    - vancomycin, n=259
- Patients similarly matched across the 3 treatment arms, but differences noted between studies in terms of age, body weight, inpatient status, and concomitant antibiotic use

*FAS: all randomized patients who received any treatment and who had any post-dose evaluation

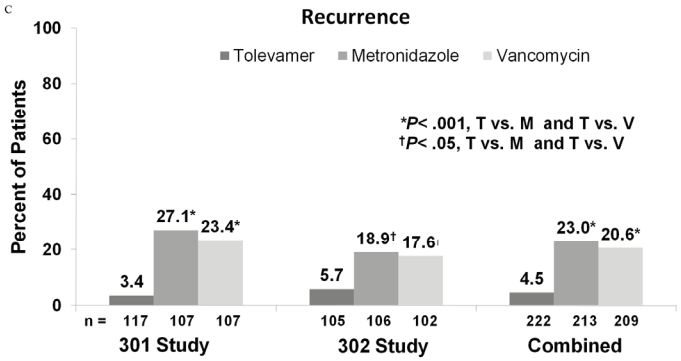
Johnson S, et al. *Clin Infect Dis.* 2014;59:345-54.

Results: Clinical Success



Johnson S, et al. *Clin Infect Dis.* 2014;59:345-54.

Results: CDI Recurrence

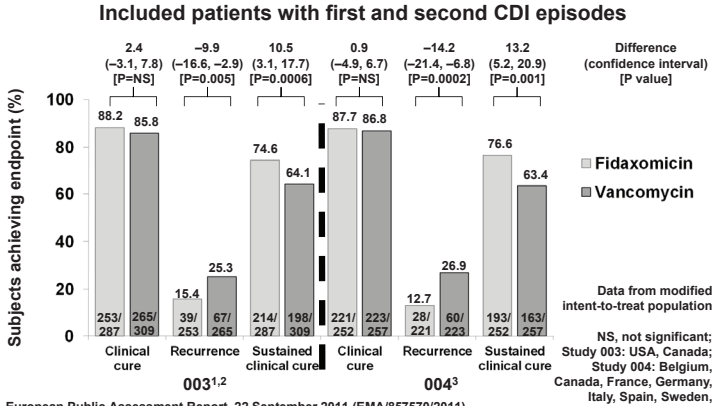


Johnson S, et al. *Clin Infect Dis.* 2014;59:345-54.

Alternative Approaches to Therapy (Recurrent CDI)

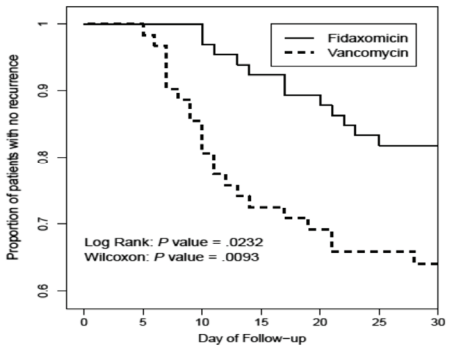
- Switch treatment agent
- Tapering/pulsed treatment regimens (vancomycin, fidaxomicin)
- Post-vancomycin chaser regimens (rifaximin, fidaxomicin)
- Host microbiota replacement (various means to deliver FMT)
- Immune approach (only anecdotal support for IVIG, but mAb will likely be available in the near future)

Phase 3 Trial Results of Fidaxomicin vs. Vancomycin for CDI



1. European Public Assessment Report, 22 September 2011 (EMA/857570/2011).
2. Louie TJ, et al. *N Engl J Med.* 2011;364:422–31.
3. Cornely OA, et al. *Lancet Infect Dis.* 2012;12:281–9.

Rate of Recurrent CDI in Patients Treated for 1st Recurrence of CDI: Randomized Substudy of Phase 3 Fidaxomicin Trials



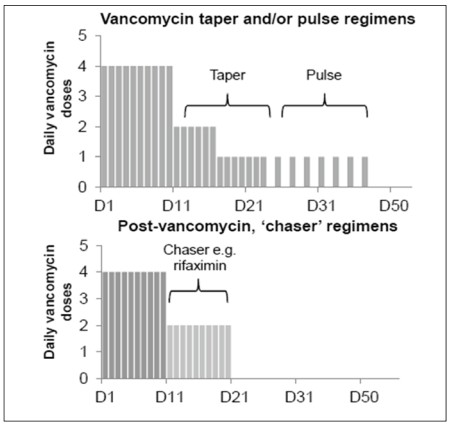
Cornely OA, et al. *Clin Infect Dis.* 2012;55 (Suppl 2):S154-61.

Caution for Using a Standard Treatment Course of Fidaxomicin in Patients with Multiple CDI Recurrences

- 2 patients with multiple recurrences given treatment doses of fidaxomicin with improvement but followed by symptomatic recurrence
- Prior regimens
  - 62 YOF: M x 14 d followed by Sb twice, V (many), V tapers (several)
  - 44 YOF: (M x 14 d twice); V x 10 d twice, rifaximin chaser

Sb, *Saccharomyces boulardii* therapy
Orenstein R. *Clin Infect Dis.* 2012;55:613-4.

Alternative Dosing Strategies for Treatment of Recurrent CDI



Alternative Fidaxomicin Dosing Regimens for Patients with Multiple CDI Recurrences

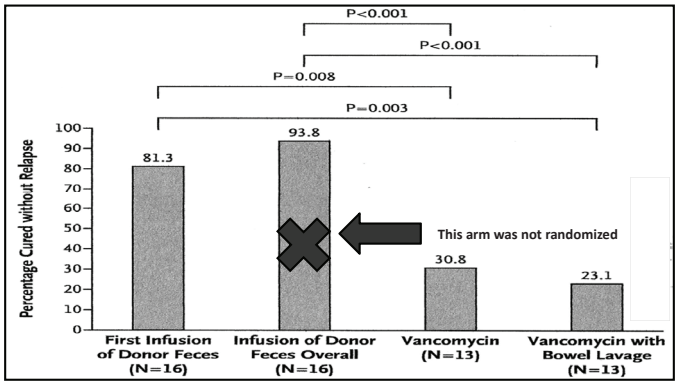
Symptom-free intervals (SFI) & subsequent recurrence rates

n	Age, mean±SD	Sex (F)	No. of CDI episodes, mean±SD	Longest SFI* prior to FDX regimen, median (IQR)	SFI* post FDX regimen median (IQR)	Subsequent recurrence rate
Fidaxomicin Chaser *(200 mg bid x 10d)*						
8	66.9±19	75%	5.5±2	57 (48)	278 (649)	38%
Fidaxomicin Taper *(200 mg daily x 7d, then q every other day x 26d)*						
12	63.6±16	58%	5.1±2	25 (30)	257 (280)**	18%

**SFI: Symptom-free interval, days*
***p=0.003, compared with non-fidaxomicin taper SFI, Mann-Whitney U test*
Treatments prior to the fidaxomicin regimens included:
metronidazole, vancomycin, rifaximin chaser, IVIG, fecal transplant, and vancomycin taper (all patients had at least 1 vancomycin taper [mean no.= 2.3])

Soriano MM. *Open Forum Infect Dis.* 2014;1(2): doi: 10.1093/ofid/ofu069.

Randomized Trial of Fecal Microbiota Transplantation (FMT)



van Nood E, et al. *N Engl J Med.* 2013;368:407-15.
Kelly CP. *N Engl J Med.* 2013; 368:474-5.

FMT Approaches

- Multiple methods of administration
  - Overall ~75% by colonoscopy or retention enema
  - ~25% by nasogastric tube or upper GI endoscopy
    - Reported efficacy >90% for lower versus >80% for upper routes
- Recent publications provide recommendations for:
  - Donor screening, processing of donor feces, methods of administration
- "Stool banks" – improve access
  [academic, not-for-profit & commercial]

Bakken JS, et al. *Clin Gastroenterol Hepatol.* 2011;9:1044-9.
Hamilton MJ, et al. *Am J Gastroenterol.* 2012;107:761-7.
Youngster I, et al. *JAMA.* 2014;312:1772-8

Emerging Approaches in Treating CDI and Reducing the Risk of Recurrence

- **Narrow-spectrum antibiotics**
  - Several new antibacterial agents under study
- **Microbial approaches**
  - FMT (pre-screened donors, capsules)
  - Biotherapeutics (e.g., non-toxigenic *C. difficile [NTCD]*)
- **Toxin binders**
  - Tolevamer or similar agent as adjunctive therapy?
- **Immune approaches**
  - Monoclonal antibodies to toxin A and B, (actoxumab/bezlotoxumab*)*

CDI Antibacterial Agents in Clinical Trials: clinicaltrials.gov

Drug	Sponsor	Drug Class	Clinical Status
CB-183,315 (surotomycin)	Merck	cyclic lipopeptide	Phase III
ACT-179811 (cadazolid)	Actelion	quinolonyl-oxazolidinone	Phase III
LFF571	Novartis	thiopeptide	Phase II
SMT19969	Summit	?	Phase II
CRS3123	NIAID	methionyl-tRNA synthetase inhibitor	Phase I

Evolution of Bacteriotherapy (FMT)

Whole fecal microbes delivered by enema, NG/NJ, colonoscopy

Whole fecal microbes in condensed form given orally, fresh, frozen, freeze dried

Modified whole fecal microbes...some components inactivated

Defined microbial mixtures of 4–33 strains

Single strains: NTCD, *C. scindens*?

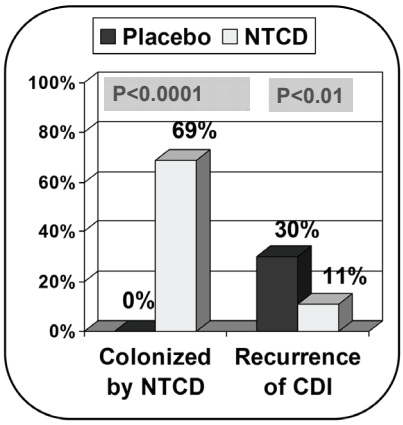
Non-toxigenic *C. difficile* Spores: Nature's Tailor-made Probiotic?

- **NTCD** **(Non-toxigenic *C. difficile*)**
  - Spores of strain VP20621
- **Protects hamsters** against colonization by toxigenic *C. difficile* and against CDI

Phase II trial:

Pts with CDI on standard treatment (vanco or metro) randomized to:

- **Placebo (n=43)**
- ***or* NTCD (Total n=125)**
  - 10^4 x 7 days (n=41)
  - 10^7 x 7 days (n=43)
  - 10^7 x 14 days (n=41)



Gerding DN, et al. *JAMA*. 2015;313:1719-27.

Phase 3 Trials of Actoxumab/Bezlotoxumab, mAbs as Adjunctive Therapy for CDI

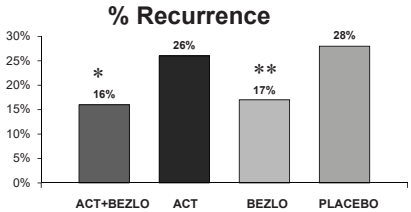
- Patients receiving standard of care for primary or recurrent CDI randomly assigned to one IV infusion of:
  - ACT+BEZ 10 mg/kg each
  - ACT 10 mg/kg alone *(MODIFY I)*
  - BEZ 10 mg/kg alone
  - Placebo
- 1º endpoint: recurrent CDI at 12 weeks
- MODIFY I
  - 1452 patients (19 countries); 1412 (97%) received study infusion
- MODIFY II
  - 1203 patients (17 countries); 1168 (97%) received study infusion

Wilcox M, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.
Gerding D, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.

Recurrent CDI Rates in Two Phase 3 Trials of Actoxumab/Bezlotoxumab

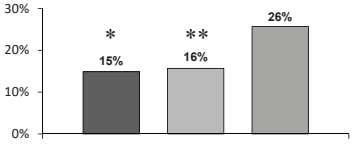
MODIFY I

***ACT+BEZLO vs Pbo: p<0.0001)**
****BEZLO vs Pbo: p=0.0003)**



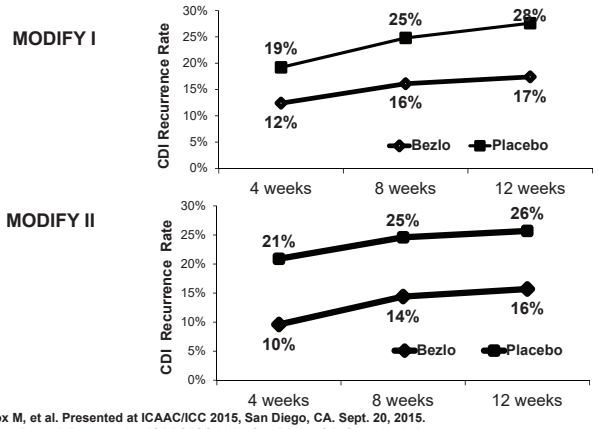
MODIFY II

***ACT+BEZLO vs Pbo: p<0.0001)**
****BEZLO vs Pbo: p=0.0003)**



Wilcox M, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.
Gerding D, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.

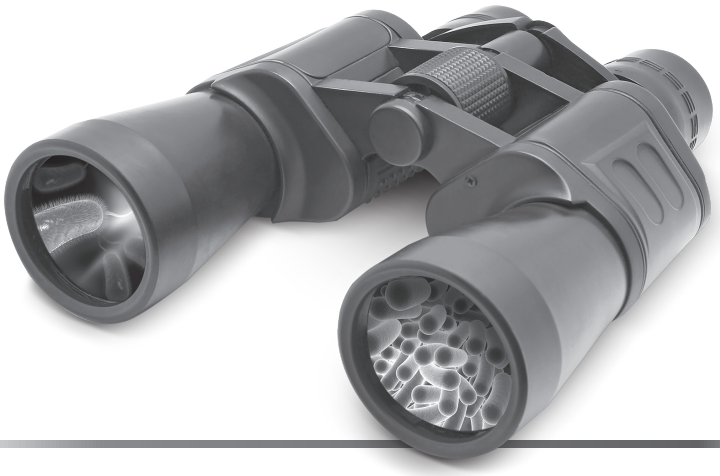
CDI Recurrence by Timepoint: Efficacy Sustained Over 12 Weeks



Wilcox M, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.
Gerding D, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.

Summary

- Accumulating data indicate that metronidazole is inferior to vancomycin for treatment of CDI
- Vancomycin and fidaxomicin are similarly effective for primary CDI and fidaxomicin is superior for sustained response
- Most patients with recurrent CDI can be managed with currently available anti-infectives (e.g., vancomycin and fidaxomicin) but novel regimens need to be used (e.g., taper, post-vancomycin chaser regimens) and patients need careful follow-up
- Unresolved issues: In what setting should fidaxomicin and FMT be used? Primary CDI, 1st , 2nd, 3rd or later recurrence?
- Potential new treatments for CDI include additional narrow-spectrum antibiotics, biotherapeutics (NTCD), and immune-based therapy (mAb)



The Growing Concern of Bacterial Infections in Hospitals: Epidemiology and Gram-Negative Resistance Mechanisms

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ID Clinical Pharmacy Coordinator
& Adjunct Associate Professor
Oregon Health and Science University
Departments of Pharmacy & Infectious Diseases
Portland, OR

Overview

- Epidemiology
- Mechanisms of resistance
- Patient risk factors for resistant infections
- Consequences of inappropriate empiric therapy

Bacterial Pathogens Representing a Threat (CDC 2013)

- **Urgent Threats**
  - ***Clostridium difficile***
  - **Carbapenem-resistant Enterobacteriaceae**
  - **Drug-resistant *Neisseria gonorrhoeae***
- **Serious Threats**
  - **MDR *P. aeruginosa* and *Acinetobacter***
  - **ESBL-producing Enterobacteriaceae**
  - **MRSA and VRE**
  - **Various drug-resistant species (*Campylobacter*, *S. pneumoniae*, *Salmonella*, tuberculosis, *Shigella*)**

CDC. Available at: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.

Antibiotic Resistance Threats in the United States, 2013

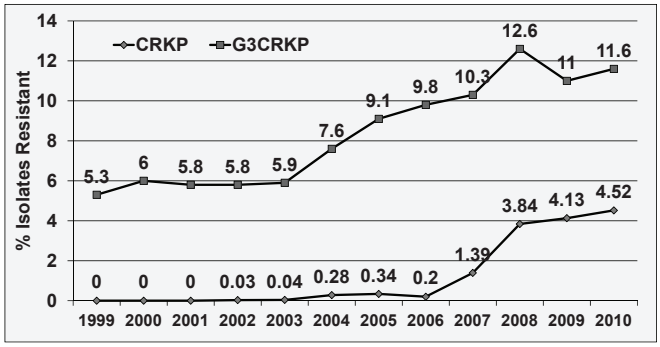
Gram-negative Organism	Cases (%)	Deaths (%)	Threat Level
ESBL-producing Enterobacteriaceae	26,000 (1.93)	1700 (7.44)	Serious
Carbapenem-resistant Enterobacteriaceae	9300 (0.69)	610 (2.67)	Urgent
Multidrug-resistant *Pseudomonas aeruginosa*	6700 (0.5)	440 (1.92)	Serious
Multidrug-resistant *Acinetobacter*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

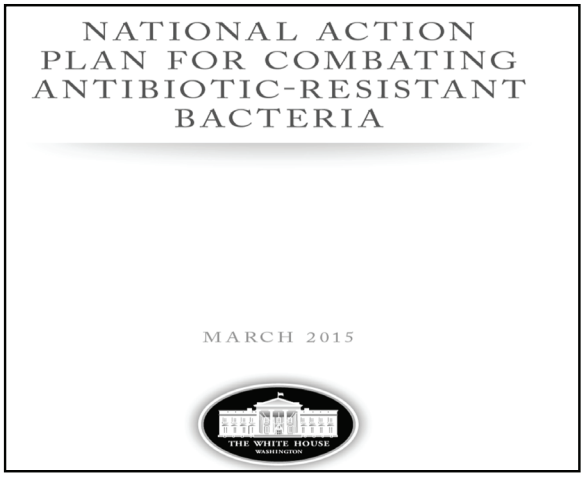
Thabit AK, et al. *Expert Opin Pharmacother.* 2015;16:159-177.
http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.

Rising Incidence of MDR Pathogens

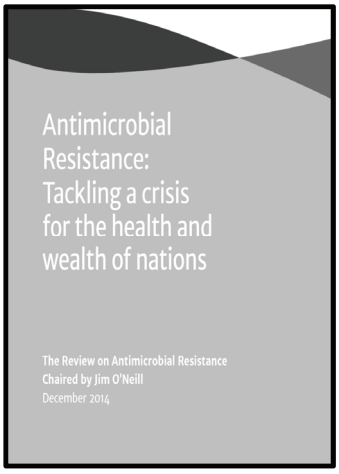
Retrospective analysis of ~500,000 *K. pneumoniae* isolates from throughout the US

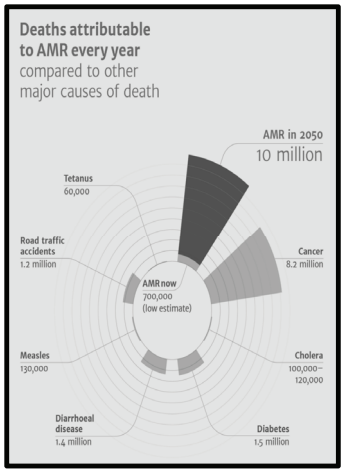


CRKP, carbapenem-resistant *K. pneumoniae*; G3CRKP, third-generation cephalosporin-resistant *K. pneumoniae*
Braykov NP, et al. *Infect Control Hosp Epidemiol.* 2013;34:259-268.



Available at: https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf - accessed 2/8/16



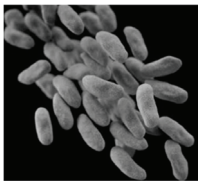


AMR, antimicrobial resistance.
The Review on Antimicrobial Resistance. http://www.his.org.uk/files/4514/1829/6668/AMR_Review_Paper_-_Tackling_a_crisis_for_the_health_and_wealth_of_nations_1.pdf. Accessed February 8, 2016.

Antibiotic-resistant Bacteria: Fast Facts

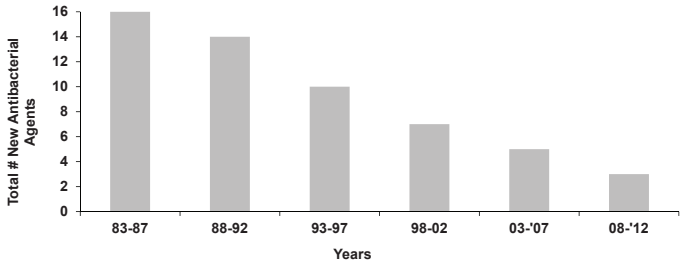
- Resistant organisms cause more than **2 million illnesses** and at least **23,000 deaths** each year in the US.
- Up to **70%** fewer patients will get CRE in 5 years if facilities coordinate to protect patients.
- Preventing infections and improving antibiotic prescribing could save **37,000 lives** from drug-resistant infections over 5 years.

INTEGRATED EFFORTS ARE KEY!!!!



CRE, carbapenem-resistant Enterobacteriaceae infection.
http://www.cdc.gov/vitalsigns/stop-spread/index.html. Accessed February 26, 2015.

FDA Reboot of Antibiotic Development: Antimicrobial Agents Approved



Shlaes DM, et al. *Antimicrob Agents Chemother*. 2013;57(10):4605-4607.

Challenges

- *E. coli* is the most common pathogen in hospitals
- ESBLs are common, clonal and spreading rapidly
- ESBLs are MDR and also XDR
- Carbapenemase-producing Enterobacteriaceae are game changers and spreading worldwide

MDR, multidrug resistant; XRD, extensively drug resistant.

Pathogens Associated with HCAIs

Pathogen	All HCAIs (N=504) Number (%)	Pneumonia (n=110)	Surgical Site Infections (n=110)	GI Infections (n=86)	UTIs (n=65)	Bloodstream Infections (n=50)
Clostridium difficile	61 (12.1)	0	0	61 (70.9)	0	0
Staphylococcus aureus	54 (10.7)	18 (16)	17 (16)	1 (1)	2 (3)	7 (14)
Klebsiella pneumoniae or *oxytoca*	**50 (9.9)**	**13 (12)**	**15 (14)**	**1 (1)**	**15 (23)**	**4 (8)**
Escherichia coli	**47 (9.3)**	**3 (3)**	**14 (13)**	**1 (1)**	**18 (28)**	**5 (10)**
Enterococcus	44 (8.7)	2 (2)	16 (15)	5 (6)	11 (17)	6 (12)
Pseudomonas aeruginosa	**36 (7.1)**	**14 (13)**	**7 (6)**	**1 (1)**	**7 (11)**	**2 (4)**
Candida spp.	32 (6.3)	4 (4)	3(3)	3 (4)	3 (5)	11 (22)

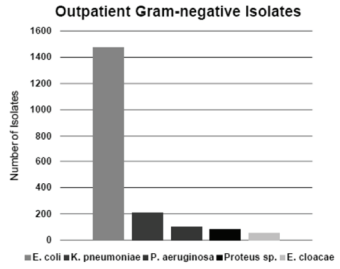
Magill SS, et al. *N Engl J Med.* 2014;370(13):1198:1208.

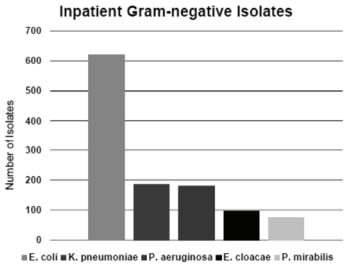
Resistance Among Gram-negatives in US Hospitals 2009–2012

	% Resistance (n) in Nonurinary Isolates			
	Intensive Care Unit (ICU)		Non-ICU	
Gram-negative	Ceftazidime-Resistant	Imipenem-Resistant	Ceftazidime-Resistant	Imipenem - Resistant
E. coli	11.0 (3084)	0.3 (3287)	6.9 (43,445)	0.1 (47,559)
K. pneumoniae	26.8 (1780)	11.5 (1907)	14.5 (16,475)	5.8 (17,228)
A. baumannii	60.1 (550)	52 (535)	35.4 (5532)	28.0 (4370)
P. aeruginosa	18.6 (2615)	23.2 (2689)	7.3 (35,210)	8.4 (35,810)

Shlaes DM, et al. *Antimicrob Agents Chemother.* 2013;57(10):4605-4607.

Oregon Health & Science University Antibiogram, 2014





INFECTION HOT TOPIC 10.1111/1469-0691.12757

The hidden epidemic of *Escherichia coli*

C.Nabet[1] and D.Raoult[2]

1) Unité de recherche sur les maladies infectieuses et tropicales émergentes, URMITE CNRS-IRD UMR 7278, and 2) URMITE UM63 CNRS 7278 IRD 198, INSERM 1095, Aix Marseille Université, Marseille, France

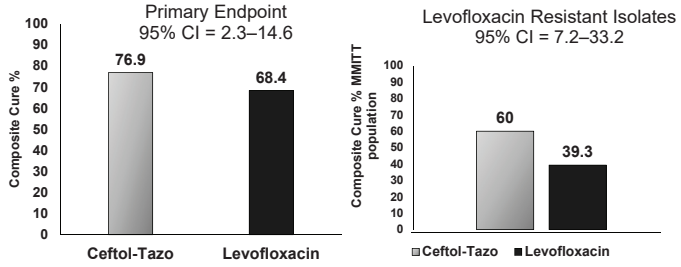
E-mail: Cecile.NABET@ap-hm.fr

Article published online: 07 July 2014

- Lifetime probability of a woman having a symptomatic UTI = 40%–50%
- Billions of resistance genes enter waste water from hospitals
- Waste water plants loaded with *E. coli* with numerous resistance genes – the bugs die, but the genes move on
- 92% of outpatient OHSU *E. coli* ceftriaxone S – 2015
- 81% of inpatient OHSU *E. coli* ceftriaxone S – 2015

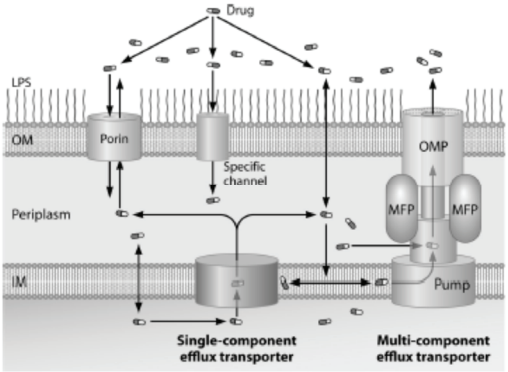
Nabet C, Raoult D. *Clin Micro Infect.* 2014;20:O792-O973.

Ceftolozane-Tazobactam vs. Levofloxacin for Complicated UTIs – Resistance Matters!



Wagenlehner FM, et al. *Lancet.* 2015;385:1949-56.

Gram-negative Resistance Mechanisms



Xian-Zhi Li, et al. *Clin Micro Rev.* 2015;28:337-418.

Mechanisms of Resistance in *P. aeruginosa*

- Quinolones
  - Reduced affinity topoisomerase 2
  - Reduced affinity topoisomerase 4
- Aminoglycosides
  - Reduced transport
  - Methylase genes
  - Modifying enzymes
- Up-regulation of efflux systems – beta-lactams
  - MexAB-OprM
  - MexCD-OprJ
  - MexEF-OprN
  - MexXY-OprM
- Porin Deletion – Carbapenems
  - OprD
- Membrane charge changes - Polymyxins
- Beta-lactamases
  - De-repression of AmpC
  - VIM/IMP/NDM metallo enzymes
  - OXA enzymes
- And the list goes on…

Livermore DM. *Clin Infect Dis.* 2002;34:634-40.

Carbapenem Resistance in Enterobacteriaceae

Enzyme	Common genetic platform	Species distribution in Enterobacteriaceae	Geographic distribution
KPC (*Klebsiella pneumoniae* carbapenemase)	*K pneumoniae* sequence type 258, various plasmids types, transposon Tn*4401*x	*K pneumoniae, Escherichia coli, Enterobacter* species, diverse Enterobacteriaceae	Endemic in the United States, Greece, Israel, Italy, Puerto Rico, China, and South America
NDM (New Delhi metallo-beta-lactamase)	Various plasmid types	*K pneumoniae* and *E coli* predominantly, diverse Enterobacteriaceae	Indian subcontinent and the Balkan region, and around the world
OXA-48 (oxacillinase)	IncI/M-type plasmid	*K pneumoniae* predominantly, diverse Enterobacteriaceae	Southern and Western Europe, Turkey and North Africa; rare in the United States
VIM (Verona integron-encoded metallo-beta-lactamase)	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in Italy, Greece, and the Far East, sporadic globally
IMP	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in the Far East and South America, sporadic globally
SME	Chromosome	*Serratia marcescens*	Sporadic in North America and South America

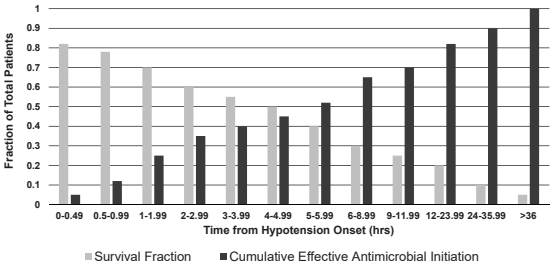
Perez F, et al. *Clev Clin J Med.* 2013;80:225-233.

Who is at Risk for Colonization and Subsequent Infections with MDR Gram-negatives?

- Previous exposure to broad-spectrum antibiotics
  - Including vancomycin
- Exposure to an increasing number of antibiotics
- Increasing age (>60 yo)
- Increasing chronic disease score
- Previous ICU stay
- COPD
- Increasing duration of hospitalization

Harris AD, et al. *Emerg Infect Dis* 2007;13:1144-9.
Papadimitriou-Olivgeris M, et al. *J Antimicrob Chemother.* 2012;67:2976-81.

Time to Effective Antibiotics & Mortality



Kumar A, et al. *Crit Care Med.* 2006;34:1589-96.

What Happens When You Run Out of Options

- KPC-producing bacteria
- 111 ICU patients in Italy, single center, septic shock
- Overall mortality: 40%
- Predictors of survival
  - Initial therapy (w/in 24h) - 2 antibiotics with in vitro activity
  - Removal of source of infection
  - Use of colistin
- Predictors of mortality
  - Colistin resistance
  - Intra-abdominal source

Falcone M, et al. *Clin Microbiol Infect.* epub ahead of print 2/2/2016 http://dx.doi.org/10.1016/j.cmi.2016.01.016

Compromise of the Last Line

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

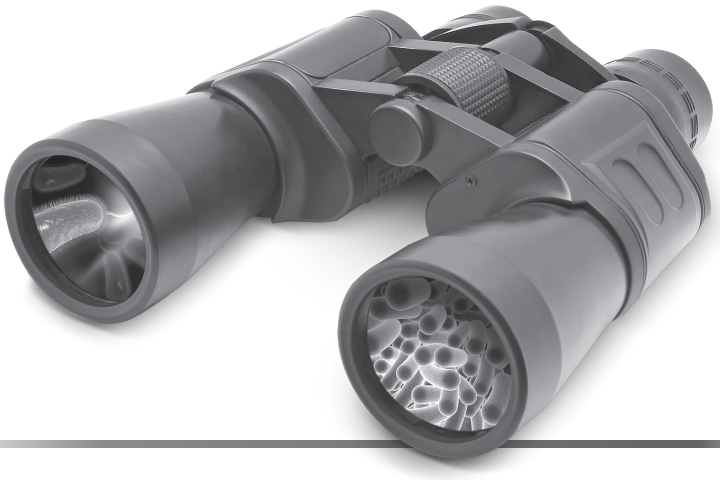
Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

- Gene easily mobilized to *E. coli, K. pneumoniae* and *P. aeruginosa*
- Adds a phosphoethanolamine to lipid A = no binding of colistin
- 78 (15%) of 523 samples of raw meat
- 166 (21%) of 804 animals during 2011–14
- 16 (1%) of 1322 samples from inpatients with infection

Liu YY, et al. *Lancet Infect Dis* 2016;16:161-8.

Conclusions

- The challenge of resistant Gram-negative bacteria is substantial
- The bugs don't stop, and they have a variety of weapons
- Antibiotic development has not kept pace, but is improving?
- Resistance often = clinical failure
- Clinical failure often = increased mortality



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

Antibiotic Treatment of Resistant Gram-negative Organisms

- Infections caused by resistant Gram-negative organisms are associated with increased morbidity and mortality compared to susceptible counterparts
- 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 broad-spectrum agent
  - monotherapy versus combination therapy
  - determining the role of adjunctive therapy

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
Carbapenem-resistant Enterobacteriaceae	9300 (0.69)	610 (2.67)	Urgent
Multidrug-resistant *Pseudomonas aeruginosa*	6700 (0.5)	440 (1.92)	Serious
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.
http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.

Which one of the following statements best describes the availability of colistin and/or polymyxin B at your institution?

1. Colistin only and anyone can prescribe it
2. Colistin only but with restrictions who can prescribe it
3. Polymyxin B only and anyone can prescribe it
4. Polymyxin B only but with restrictions who can prescribe it
5. Both agents and anyone can prescribe it
6. Both agents but with restrictions who can prescribe it
7. I don't know

Colistin and Polymyxin B

- Assumed an important role as "salvage therapy" for otherwise untreatable Gram-negative infections
- Emerging pharmacokinetic/pharmacodynamic data indicate that monotherapy is unlikely to generate plasma concentrations that are reliably efficacious
- Regrowth and the emergence of resistance with monotherapy are commonly reported even when concentrations exceed those achieved clinically
- Combination therapy has been suggested as a possible means of increasing antimicrobial activity and reducing the development of resistance

Bergen PJ, et al. *Pharmacother.* 2015;356:34-42.

Combination Antibiotic Treatment of Resistant Gram-negative Organisms

- Choice of agents often involves:
  - Aminoglycosides
  - Beta-lactam/beta-lactamase inhibitors
  - Carbapenems
  - Fosfomycin
  - Polymyxins
  - Rifampin
  - Tetracyclines
  - Tigecycline
- Clinical evidence regarding effectiveness of different treatment regimens is principally derived from retrospective studies, case reports or small prospective studies; no randomized clinical trials
- Need for new antimicrobial agents to treat resistant Gram-negative organisms is inevitably important

Agents Being Developed to Treat Resistant Gram-negative Bacteria

Agent	Related-Class	Developer
Ceftolozane-Tazobactam	BLBLI	Merck
Ceftazidime-Avibactam	BLBL	Allergan
Meropenem-RPX7009	BLBLI	Medicines Company
Imipenem-Relebactam	BLBLI	Merck
Aztreonam-Avibactam	BLBLI	AstraZeneca
S649266	Cephalosporin	Shionogi
Eravacycline	Tetracycline	Tetraphase
Plazomicin	Aminoglycoside	Achaogen
POL7080	Macrocycle LptD Inhibitor	Roche / Polyphor

BLBLI, Beta-lactam/beta-lactamase inhibitor combinations

Beta-lactamase Inhibitor Revival

New Hope for Old Antibiotics

- **Tazobactam**
  - **2:1 ratio ceftolozane:tazobactam (FDA approval)**
- **Avibactam (NXL-104) and Relebactam (MK-7655)**
  - **Novel diazabicyclooctane class**
  - **4:1 ratio ceftazidime:avibactam (FDA approval)**
  - **2:1 and 4:1 imipenem:relebactam**
- **RPX7009**
  - **Boron-containing serine beta-lactamase inhibitor**
  - **1:1 ratio meropenem:RPX7009**

Garber K. *Nature Rev Drug Discovery.* 2015;14:445-447.
Drawz SM, et al. *Antimicrob Agents Chemother.* 2014;58:1835-1846.
Olsen I. *Eur J Clin Microbiol Infect Dis.* 2015;34:1303-1308 .

Ambler Classification (Beta-lactamases)

Ambler Class	Beta-lactamase Type	Preferred Substrates	Representative Enzymes
A	Narrow-spectrum	Penicillins, narrow-spectrum cephalosporins	TEM-1, TEM-2, SHV-1
A	Extended-spectrum	Narrow and extended-spectrum beta-lactams	SHV-2, CTX-M-15, PER-1, VEB-1
A	Serine-carbapenemase	Carbapenems	KPC-1, IMI-1, SME-1
B	Metallo-beta-lactamases	Most beta-lactams, including carbapenems	VIM-1, IMP-1, NDM-1
C	Cephalosporinases	Cephalosporins	AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1
D	OXA-type enzymes	Penicillins, oxacillins, carbapenems	OXA enzymes

Drawz SM, Bonomo RA. *Rev Clin Microbiol Rev.* 2010;14:160-201.
Toussaint KA, Gallagher JC. *Ann Pharmacother.* 2015;49:86-98.

Spectrum of Beta-lactamase Inhibitors

Spectrum	Beta-lactamase Inhibitor			
	Tazobactam	Avibactam	RPX7009	Relebactam
Class A narrow-spectrum	X	X	X	X
Class A ESBLs	X	X	X	X
Class A carbapenemases		X	X	X
Some class C enzymes	X	X	X	X
Some class D enzymes		X		

Drawz SM, Bonomo RA. *Rev Clin Microbiol Rev.* 2010;14:160-201.
Toussaint KA, Gallagher JC. *Ann Pharmacother.* 2015;49:86-98.

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S649266	Cephalosporin	Shionogi
Eravacycline	Tetracycline	Tetraphase
Plazomicin	Aminoglycoside	Achaogen
POL7080	Macrocycle LptD Inhibitor	Roche / Polyphor

BLBLI, Beta-lactam/beta-lactamase inhibitor combinations

Which one of the following statements best describes the availability of ceftolozane-tazobactam (Zerbaxa™) and/or ceftazidime-avibactam (Avycaz™) at your institution?

1. Ceftolozane-tazobactam only and anyone can prescribe it
2. Ceftolozane-tazobactam only but with restrictions who can prescribe it
3. Ceftazidime-avibactam only and anyone can prescribe it
4. Ceftazidime-avibactam only but with restrictions who can prescribe it
5. Both agents, and anyone can prescribe it
6. Both agents but with restrictions who can prescribe it
7. I don't know

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, including Pyelonephritis
  - Complicated Intraabdominal Infections (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 are nausea, diarrhea, headache, and pyrexia

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

Ceftolozane-Tazobactam

- Demonstrated *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 (μg/mL)		
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

Ceftolozane and tazobactam for injection, for intravenous use - prescribing information, July 2015.
Takeda S, et al. *Int J Antimicrob Agents.* 2007;30:443-445.
Takeda S, et al. *Antimicrob Agents Chemother.* 2007;51:826-830.
Castanheira M, et al. *Antimicrob Agents Chemother.* 2014;58:6844-6850.

Ceftolozane-Tazobactam

Antimicrobial susceptibility patterns of *Pseudomonas aeruginosa* isolates from patients hospitalized with pneumonia stratified by geographic region (2012):

	% Susceptible	
	USA (CLSI) n = 500	Europe (EUCAST) n = 519
Ceftolozane–tazobactam*	99.4	89.0
Ceftazidime	82.0	65.5
Piperacillin–tazobactam	76.2	63.0
Meropenem	80.6	67.1
Levofloxacin	76.6	54.7
Gentamicin	87.0	74.6
Amikacin	97.4	82.3

* Percentage inhibited at ceftolozane-tazobactam MICs ≤8 μg/mL; for comparison purposes only
% Multidrug-resistant (MRD): USA = 16.4%; Europe = 31.5%
% Extensively drug-resistant (XDR): USA = 8.8%; Europe = 25.1%

Farrel DJ, et al. *Int J Antimicrob Agents.* 2014;43:533-539.

Ceftolozane-Tazobactam

Ceftolozane-tazobactam activity tested against *Pseudomonas aeruginosa* isolates from patients hospitalized with pneumonia (USA - 2012)

	Cumulative (%) inhibited at MIC in μg/mL of:			MIC_{50} / MIC_{90} (μg/mL)
	4	8	16	
Pseudomonas aeruginosa (n=1019)	92.6	94.1	94.6	0.5 / 4
Ceftazidime-non-S (n=269)	72.1	77.7	79.6	4 / >32
Cefepime-non-S (n=239)	70.7	77.0	79.1	4 / >32
Meropenem-non-S (n=268)	75.7	78.0	79.9	2 / >32
Piperacillin-tazobactam-non-S (n=311)	76.5	81.4	83.0	2 / >32
CAZ & MEM & P/T-non-S (n=158)	60.1	63.9	67.1	4 / >32
Levofloxacin-non-S (n=307)	81.4	82.7	84.4	2 / >32
Gentamicin-non-S (n=197)	71.6	73.1	75.1	2 / >32
Multidrug-resistant (MDR) (n=246)	72.4	75.6	77.6	2 / >32
Extensively drug-resistant (XDR) (n=174)	63.2	66.1	69.0	4 / >32

Farrel DJ, et al. *Int J Antimicrob Agents.* 2014;43:533-539.

Ceftolozane-Tazobactam

- Isolates displaying derepressed AmpC had ceftolozane-tazobactam MIC values ranging from 1 to 16 µg/mL[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;58:6844-6855.
[2] Cabot G, et al. *Antimicrob Agents Chemother.* 2014;58:3091-3099.
[3] Berrazeg M, et al. *Antimicrob Agents Chemother.* 2015;59:6248-6255.

Ceftolozane-Tazobactam

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- FDA approval in December 2014
  - Complicated Urinary Tract Infections, including Pyelonephritis
  - Complicated Intraabdominal Infections (plus metronidazole)
  - IV dose: 1.5 g (1 g ceftolozane; 0.5 g tazobactam) q8h (1-h infusion)
- Ongoing Phase 3 Trial: Ventilated nosocomial pneumonia; ***increased dose***: 3.0 g (2 g ceftolozane; 1 g tazobactam) q8h
  - For 8 days; however 14 days for *Pseudomonas aeruginosa*
- Plasma-to-epithelial lining fluid penetration ~50%

Zhanel GG, et al. *Drugs.* 2014;74:31-51.
Chandorkar G, et al. *J Antimicrob Chemother.* 2012;67:2463-2469.
ClinicalTrials.gov: NCT02070757

Ceftolozane–Tazobactam Therapy* of Respiratory Infections due to 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) Ciprofloxacin (>2) Tobramycin (<2) Piperacillin-Tazobactam (<16)
63 y; male	Meropenem, Ciprofloxacin	Cure / Eradication	Ceftolozane-Tazobactam (1) Meropenem (>8) Cefepime (>16) Ciprofloxacin (>2) Tobramycin (>8) Piperacillin-Tazobactam (>64) Colistin (susceptible) Polymyxin (susceptible)
52 y; Male	Meropenem, Linezolid	Cure / Eradication	Ceftolozane-Tazobactam (1) Meropenem (>8) Cefepime (16) Ciprofloxacin (<0.5) Tobramycin (<2) Piperacillin-Tazobactam (>16)

*Ceftolozane–tazobactam 3 g IV every 8 hours for 14 days

Gelfand MS & Cleveland KO. *Clin Infect Dis.* 2015;61:853-855 [letter to editor].

Ceftazidime-Avibactam

- Antipseudomonal cephalosporin plus beta-lactamase inhibitor
- Spectrum of activity: Gram-negatives, including MDR *Pseudomonas aeruginosa*, ESBL-producing strains, KPCs
- FDA approval in February 2015 (based on Phase 2 data)
  - Complicated Urinary Tract Infections, including Pyelonephritis
  - Complicated Intraabdominal Infections (plus metronidazole)
  - IV dose: 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)
  - For patients with limited or no alternative treatment options
- Dosage adjustment in patients with CrCl ≤50 mL/min
- Most common adverse reactions are vomiting, nausea, constipation, and anxiety

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 (µg/mL)	
Pathogen	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

Ceftazidime and avibactam for injection, for intravenous use - prescribing information, September 2015.

Ceftazidime-Avibactam

Antimicrobial susceptibility patterns of *Pseudomonas aeruginosa* isolates from intensive care unit (ICU) and non-ICU patients from US Hospital (2012–2013):

	% Susceptible	
	ICU n = 842	Non-ICU n = 2240
Ceftazidime–avibactam*	95.6	97.5
Ceftazidime	77.7	86.9
Cefepime	79.8	86.1
Piperacillin–tazobactam	71.2	82.2
Meropenem	76.6	84.7
Levofloxacin	76.4	75.4
Amikacin	98.6	97.9
Colistin	100.0	99.9

*Percentage inhibited at ceftazidime-avibactam MICs ≤8 µg/mL

Sader HS, et al. *Int J Antimicrob Agents*. 2015;46:53-59.

Ceftazidime-Avibactam

Ceftazidime-avibactam activity tested against *Pseudomonas aeruginosa* isolates from patients hospitalized in USA (2012–2013):

	Cumulative (%) inhibited at MIC in µg/mL of:			MIC_{50} / MIC_{90} (µg/mL)
	4	8	16	
Pseudomonas aeruginosa (n=3082)	91.7	97.0	99.0	2 / 4
non-ICU (n=2240)	93.2	97.5	99.2	2 / 4
ICU (n=842)	87.9	95.6	98.3	2 / 4
VAP (n=185)	92.4	97.3	100.0	2 / 4
Ceftazidime-non-S (n=482)	60.2	80.7	93.4	4 / 16
Meropenem-non-S (n=537)	67.8	87.0	95.3	4 / 16
Multidrug-resistant (MDR) (n=436)	57.3	80.7	93.1	4 / 16
Extensively drug-resistant (XDR) (n=247)	46.6	74.5	89.1	8 / 32

Sader HS, et al. *Int J Antimicrob Agents.* 2015;46:53-59.

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;59:1020-1029.

Ceftazidime-Avibactam

- Spectrum of activity: Gram-negatives, including MDR *Pseudomonas aeruginosa*, ESBL-producing strains, KPCs
- FDA approval in February 2015 (based on Phase 2 data)
  - Complicated Urinary Tract Infections, including Pyelonephritis
  - Complicated Intraabdominal Infections (plus metronidazole)
  - For patients with limited or no alternative treatment options
  - IV dose: 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)
- Clinical trials: Nosocomial pneumonia - Dose of 2.5 g q8h
- Plasma-to-epithelial lining fluid penetration ~30%

Liscio JL, et al. *Int J Antimicrob Agents.* 2015;46:266-271.
Nicolau D, et al. *J Antimicrob Chemother.* 2015;70:2862-2869.
ClinicalTrials.gov: NCT01808092.

Agents Being Developed to Treat Resistant Gram-negative Bacteria

Agent	Related-Class	Developer
Ceftolozane-Tazobactam	BLBLI	Merck
Ceftazidime-Avibactam	BLBLI	Allergan
Meropenem-RPX7009	BLBLI	Medicines Company
Imipenem-Relebactam	BLBLI	Merck
Aztreonam-Avibactam	BLBLI	AstraZeneca
S649266	Cephalosporin	Shionogi
Eravacycline	Tetracycline	Tetraphase
Plazomicin	Aminoglycoside	Achaogen
POL7080	Macrocycle LptD Inhibitor	Roche / Polyphor

BLBLI, Beta-lactam/beta-lactamase inhibitor combinations

In Vitro Activity of Meropenem–RPX7009

4,500 isolates collected from 11 hospitals in Brooklyn and Queens, NY from November 2013 to January 2014

Species (n)	Meropenem		Meropenem-RPX7009 (4 µg/mL)		Meropenem-RPX7009 (8 µg/mL)	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Klebsiella pneumoniae (KPC+) (121)	8	64	0.06 / 4	2 / 4	0.03 / 8	0.5 / 8
Pseudomonas aeruginosa (98)	8	32	8 / 4	32 / 4	8 / 8	32 / 8
Acinetobacter baumannii (84)	32	64	32 / 4	64 / 4	32 / 8	64 / 8

MIC values in µg/mL

- Addition of RPX7009 resulted in a 64- to 512-fold decrease in meropenem MIC in majority of KPC-positive isolates
- All but 2 of these isolates (98.3%) were inhibited by 1 µg/mL meropenem combined with RPX7009 at 8 µg/mL

Lapuebla A, et al. *Antimicrob Agents Chemother.* 2015;59:4856-4860.

Meropenem-RPX7009

- *In vitro* hollow-fiber model (simulating human exposure of 2 g meropenem plus 2 g RPX7009 dose q8h and infused over 3 hours) demonstrated bactericidal activity against KPC-producing isolates of Enterobacteriaceae
- *In vivo* efficacy in murine thigh infection model against KPC-producing isolates of *K. pneumoniae*, *E. coli*, and *E. cloacae* (MICs ranging from ≤0.06 to 8 µg/mL)
- Agents display identical concentration-time profiles with each other in plasma and in epithelial lining fluid
- Clinical trials evaluating the efficacy, safety, and tolerability in adults with serious infections due to carbapenem-resistant Enterobacteriaceae are ongoing

ICAAC 2014 (abstr. F-959 & F-958).
Wenzler E, et al. *Antimicrob Agents Chemother.* 2015;59:7232-7239.
Clinicaltrials.gov: NCT02166476 & NCT02168946.

In Vitro Activity of Imipenem-Relebactam

4,000 isolates collected from 11 hospitals in Brooklyn and Queens, NY from November 2013 to January 2014

Species (n)	Imipenem		Imipenem-Relebactam	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Escherichia coli (2778)	0.25	0.25	0.25 / 4	0.25 / 4
Klebsiella pneumoniae (891)	0.25	4	0.25 / 4	0.25 / 4
bla_{KPC}-possessing *K. pneumoniae* (111)	16	>16	0.25 / 4	1 / 4
Enterobacter spp. (211)	0.5	1	0.25 / 4	0.5 / 4
Pseudomonas aeruginosa (490)	2	16	0.5 / 4	2 / 4
Imipenem-resistant *P. aeruginosa* (144)	8	>16	1 / 4	2 / 4
Acinetobacter baumannii (158)	4	>16	2 / 4	>16 / 4
bla_{OXA-23}-possessing *A. baumannii* (58)	>16	>16	>16 / 4	>16 / 4

MIC values in µg/mL

Lapuebla A, et al. *Antimicrob Agents Chemother.* 2015;59:5029-5031.

Plazomicin (ACHN-490)

- Next-generation aminoglycoside ("neoglycoside") synthetically derived from sisomicin
- Inhibits bacterial protein synthesis and exhibits dose-dependent bactericidal activity
- *In vitro* activity against both Gram-positive and Gram-negative organisms, including isolates harboring any of clinically relevant aminoglycoside-modifying enzymes (e.g., acetyltransferases, nucleotidyltransferases, and phosphotransferases)
- *In vitro* synergy activity when combined with cefepime, doripenem, imipenem or piperacillin-tazobactam against *Pseudomonas aeruginosa*
- After IV 15 mg/kg dose, maximum plasma concentration ~113 µg/mL, AUC_{0-24} of 235 µg•h/mL, $t_{1/2}$ of 4 hours, and apparent V_{ss} of 0.25 L/kg
- Human studies have not reported nephrotoxicity or ototoxicity, and lack of ototoxicity in the guinea pig model

Zhanel GG, et al. *Expert Rev Anti Infect Ther.* 2012;10:459-473.
Cass RT, et al. *Antimicrob Agents Chemother.* 2011;55:5874-5880.

Plazomicin

***In vitro* activity of plazomicin against aminoglycoside-susceptible and non-susceptible *Pseudomonas aeruginosa*:**

	Cumulative (%) inhibited at MIC in µg/mL of:									
	≤0.25	0.5	1	2	4	8	16	32	64	>64
Amikacin-S (n=561)	2.7	4.1	10.7	38.3	71.1	90.6	98.8	100		
Gentamicin-S (n=529)	2.6	4.2	11.2	40.6	74.5	93.6	99.6	100		
Tobramycin-S (n=560)	2.5	3.9	10.5	38.0	70.0	88.2	95.7	98.6	100	
Amikacin-non-S (n=32)	0	0	0	6.3	6.3	12.5	15.6	46.9	75.0	100
Gentamicin-non-S (n=64)	1.6	1.6	1.6	3.1	10.9	26.6	50.0	73.4	87.5	100
Tobramycin-non-S (n=33)	3.0	3.0	3.0	12.1	27.3	54.5	69.7	72.7	75.8	100

- Landman et al: plazomicin MIC_{50} = 8 µg/mL and MIC_{90} = 32 µg/mL for 679 isolates of *P. aeruginosa* (amikacin: MIC_{50} = 8 µg/mL and MIC_{90} = 16 µg/mL)
- Mechanisms resulting in elevated MICs poorly defined; likely that reduced permeability and/or efflux are contributing factors

Walkty A, et al. *Antimicrob Agents Chemother.* 2014;58:2554-2563.
Landman D, et al. *J Antimicrob Chemother.* 2011;66:332-334.

Plazomicin

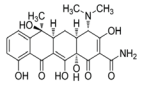
- **A Phase 3, Multicenter, Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Colistin in Patients with Infection Due to Carbapenem-Resistant Enterobacteriaceae (CRE) [CARE]**
  - **Plazomicin in combination with meropenem or tigecycline**
  - **Colistin in combination with meropenem or tigecycline**
  - **Treatment of patients with bloodstream infection, hospital-acquired or ventilator-associated bacterial pneumonia**
- **A Phase 3, Randomized, Multicenter, Double-Blind Study to Evaluate the Efficacy and Safety of Plazomicin Compared with Meropenem Followed by Optional Oral Therapy for the Treatment of Complicated Urinary Tract Infection, including Pyelonephritis, in Adults**

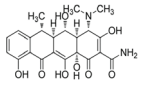
ClinicalTrials.gov: NCT01970371
ClinicalTrials.gov: NCT02486627

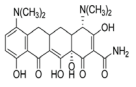
Combination Antibiotic Treatment of Resistant Gram-negative Organisms

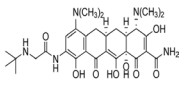
- **Choice of agents often involves:**
  - **Aminoglycosides**
  - **Beta-lactam/beta-lactamase inhibitors**
  - **Carbapenems**
  - **Fosfomycin**
  - **Polymyxins**
  - **Rifampin**
  - **Tetracyclines**
  - **Tigecycline**
- **Clinical evidence regarding effectiveness of different treatment regimens is principally derived from retrospective studies, case reports or small prospective studies; no randomized clinical trials**
- **Need for new antimicrobial agents to treat resistant Gram-negative organisms is inevitably important**

Generations of Tetracycline Antibiotics


Tetracycline


Doxycycline


Minocycline


Tigecycline

- **Doxycycline and Minocycline**
- **Discovery of "glycylcyclines" in the early 1990s**
  - **Evade most bacterial efflux pumps**
  - **Not affected by TetM ribosomal protection mechanism**
- **Tigecycline approved by FDA in 2005 as an intravenous broad-spectrum antibacterial agent**

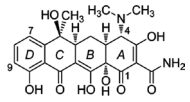
Pucci MJ and Bush K. *Clin Microbiol Rev.* 2013;26:792-821.

Tigecycline Treatment of Resistant Gram-negative Organisms

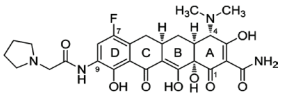
- Carbapenemase-producing Enterobacteriaceae and MDR *Acinetobacter* spp.
- Tigecycline has a large volume of distribution and low concentrations in blood, epithelial lining fluid of the lungs, and urinary tract
- Higher intravenous doses of tigecycline (100 mg every 12 hours) has resulted in better clinical cure rate, especially in critically ill patients with severe infections, including MDR bacteria

Doi Y and Paterson DL. *Semin Respir Crit Care Med.* 2015;36:74-84.
De Pascale G, et al. *Crit Care.* 2014;18:R90.
Garnacho-Montero J and Ferrandiz-Millon C. *Crit Care.* 2014;18:157.

Eravacycline: A Fluorocycline



Tetracycline



Eravacycline

- Fully synthetic fluorocycline with broad-spectrum activity including MDR Gram-positive, Gram-negative, aerobic and anaerobic organisms (reduced activity against *Pseudomonas aeruginosa* and *Burkholderia cenocepacia*)
- Active against isolates containing tetracycline-specific efflux (TetA and TetB) and ribosomal protection proteins (TetM and TetO)
- Active against Enterobacteriaceae harboring ESBLs and carbapenemases
- Intravenous and oral formulations

Pucci MJ and Bush K. *Clin Microbiol Rev* 2013; 26: 792-821

In Vitro Activity of Eravacycline

- 4,000 isolates collected from 11 hospitals in Brooklyn and Queens, NY from November 2013 to January 2014
- Broth microdilution (eravacycline, tigecycline) and agar dilution (all other agents) using CLSI standards

Species (n)	ESBL	bla_{KPC}	bla_{OXA}	Eravacycline MIC_{50}/MIC_{90}	Tigecycline MIC_{50}/MIC_{90}
E. coli (2,866)	13%	0.17%	-	0.12 / 0.5	4 / >16
K. pneumoniae (944)	33%	13%	-	0.25 / 1.0	0.5 / 2.0
Enterobacter aerogenes (90)	22%	3.3%	-	0.25 / 1.0	0.5 / 2.0
Enterobacter cloacae (124)	23%	3.2%	-	0.5 / 1.0	0.5 / 2.0
Acinetobacter baumannii (158)	67%	0.63%	36%	0.5 / 1.0	2.0 / 4.0

MIC values in µg/mL

Abdallah M, et al. *Antimicrob Agents Chemother.* 2015;59:1802-1805.

How Useful Will These New Agents be in the Future?

- New agents for treatment of Gram-negative infections are promising and could help preserve and enhance our antibiotic armamentarium
- These agents may provide opportunities for monotherapy of resistant Gram-negative organisms
- These advantages will need to be evaluated and compared to older and generic agents in regards to the use of healthcare resources and patient outcomes
- Results from randomized controlled trials are needed in severely ill patients with resistant Gram-negative infections for both older and newer agents and as monotherapy and combination therapy