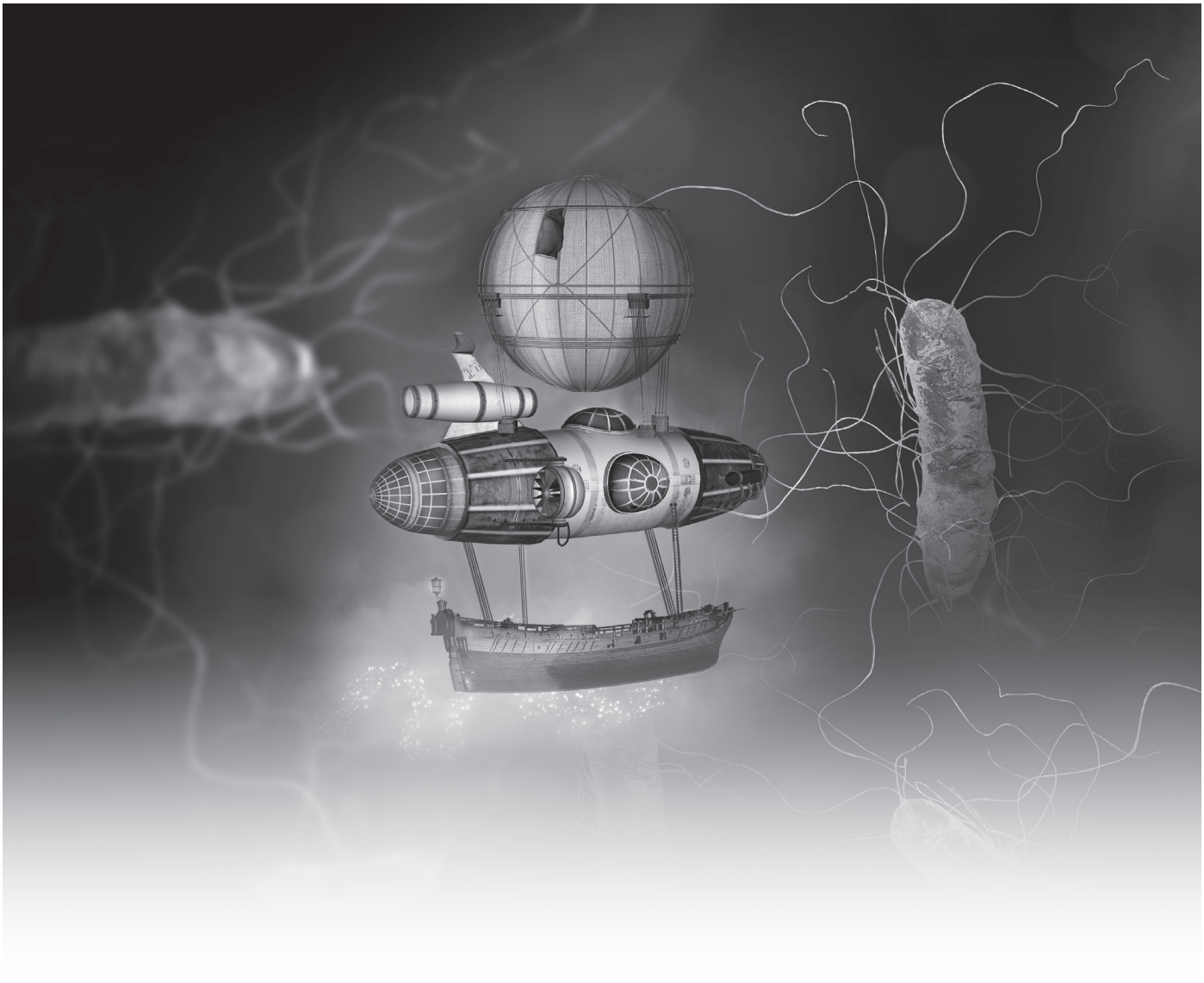

Latest Approaches in Treating *C. difficile Infection* and Preventing Recurrence: The Guidelines Have Arrived!

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Professor of Pharmacy Practice
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University of Houston
Houston, TX

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD

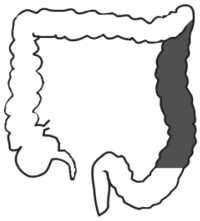
Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

Kevin W. Garey,[2] Dale N. Gerding,[3] Stuart Johnson,[3,5] Johan S. Bakken,[4] Karen C. Carroll,[5] Susan E. Coffin,[6] Erik R. Dubberke,[7] ... Gould,[1] Ciaran Kelly,[8] Vivian Loo,[9] Julia Shaklee Sammons,[1] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

Side Note: Nomenclature Changes

CLSI AST News Update. 2018;3(1):1-21.

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	Ridinilazole	Toxoid vaccines

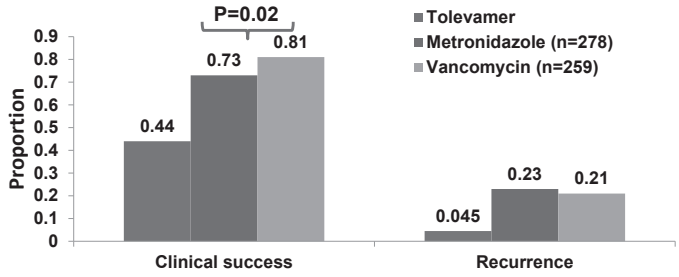
IDSA CDI Guidelines 2010

Episode	Clinical Signs	Severity	Recommended agent	Dosing Regimen	Strength of Recommendation
Initial	WBC <15,000 and SrCr <1.5 × premorbid level	Mild or moderate	Metronidazole	500 mg PO three times daily 10–14 days	A-I
Initial	WBC ≥15,000 or SrCr ≥1.5 × premorbid level	Severe	Vancomycin	125 mg PO four times daily 10–14 days	B-I
Initial	Hypotension, shock, ileus, megacolon	Severe, complicated	Vancomycin + metronidazole IV	Vancomycin: 500 mg PO or NG 4× daily + Metronidazole: 500 mg IV q8h. For ileus, consider adding rectal instillation of vancomycin	C-III
Second (1st recurrence)	----------	----------	Same as initial	Same as initial	A-II
Third (2nd recurrence)	----------	----------	Vancomycin	PO tapered and/or pulsed	B-III

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

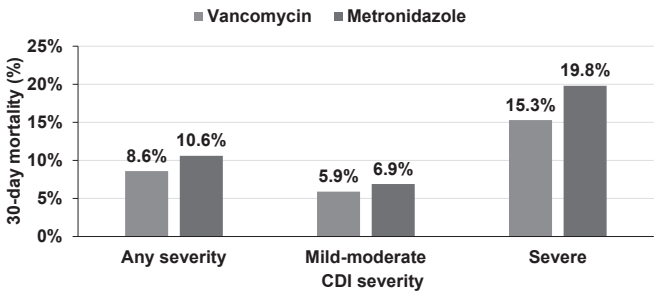
Metronidazole versus Vancomycin (Tolevamer Phase III RCT)

More recently, metronidazole has been shown to be globally inferior to vancomycin.



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.

Summary of Metronidazole vs. Vancomycin Clinical Studies

Study	Year	Location	n	Single center	Blinded	Randomized	Metro dose	Vanco dose	Clinical failure		Recurrence	
									metro	vanco	metro	vanco
Teasley, 1983	82-83	MN	101	yes	no	yes	250 mg QID	500 mg qid	2 of 37 (5.4%)	0 of 45 (0%)	2 of 37 (5.4%)	6 of 45 (13%)
Wenisch, 1996	93-95	Austria	62	yes	no	yes	500 mg TID	500 mg tid	2 of 31 (6%)	2 of 31 (6%)	5 of 31 (16%)	5 of 31 (16%)
Musher, 2006	02-04	USA (Houston)	34	no	yes	yes	250 mg QID	125 mg qid	6 of 34 (17%)	N/A	9 of 28 (32%)	N/A
Zar, 2007	94-02	Chicago	150	Yes	yes	yes	250 mg QID	125 mg qid	13 of 79 (16%)	2 of 71 (3%)	9 of 66 (14%)	5 of 69 (7%)
Johnson, 2013	05-07	World	552	no	yes	yes	375 mg QID	125 mg qid	76 of 278 (27%)	49 of 259 (19%)	48 of 202 (23%)	43 of 210 (21%)

There May Have Been MIC Creep With Metronidazole Over the Decades

Author	Location	Time period	Isolates	Metronidazole		
				MIC_{50}	MIC_{90}	Range
All strains						
Hecht et al	Various	1983–2004	110	0.125	0.25	0.025–0.5
Edlund et al	Sweden	1998	50	0.125	0.25	0.125–0.25
Betriu et al	Spain	2001	55	0.5	1	≤0.06–1
Citron et al	USA	2003	18	0.5	1	0.25–1
Finegold et al	USA (CA)	2003	72	0.5	1	0.25–2
Karlowsky et al	Canada (Manitoba)	2007	208	0.5	1	0.25–4
Debast et al	Europe	2008	398	0.25	0.5	<0.06-2
Reigadas et al	Spain	2013	100	0.25	0.5	0.06-1
Snydman et al	USA	2011-12	925	1	2	<0.06-4
BI/027/NAP1 strains						
Citron et al	USA	2004–2005		NR	2	0.5–2
Debast et al	Europe	2008		0.5	1	0.5-1
Snydman et al	USA	2011-12		2	2	<0.06-4

Shah D, et al. *Expert Rev Anti Infect Ther*. 2010;8:555-64.

Bottom Line: This May Simply be a PK/PD Problem

- Mean concentrations of metronidazole in stool: <0.25–9.5 μg/g
- MIC_{50}: 1 μg/mL MIC_{90}: 2 μg/mL
  - May be higher
- A poor response rate to metronidazole should be expected given these numbers!

Bolton RP, Culshaw MA. *Gut.* 1986;27:1169-72.

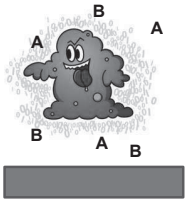
Recommendation for Initial Treatment of CDI in Adults

Clinical definition	Supportive clinical data	Recommended treatment
Initial episode, non-severe	WBC <15,000 cells/mL and serum creatinine <1.5 mg/dL	VAN 125 mg given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days Alternative if above agents are not available: metronidazole 500 mg three times daily by mouth for 10 days
Initial episode, severe	WBC ≥15,000 cells/mL or a serum creatinine >1.5 mg/dL	VAN 125 mg given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	VAN 500 mg given four times daily by mouth or nasogastric tube. If ileus, consider adding rectal instillation of VAN. Add intravenous metronidazole 500 mg every 8 hrs if ileus present

VAN: vancomycin, FDX: fidaxomicin; SD: standard dose

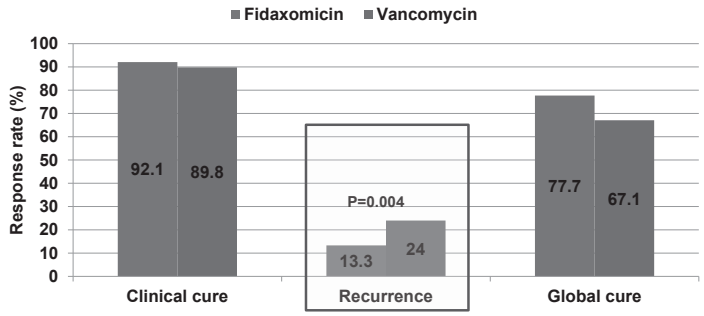
McDonald LC, et al. *Clin Infect Dis.* 2018;66(7):e1-e48.

Explosion in Treatment Possibilities for CDI Minus 1



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	Ridinilazole	Toxoid vaccines

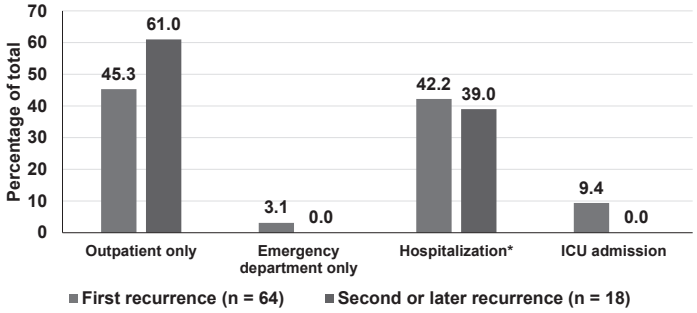
Fidaxomicin: Equal Efficacy as Vancomycin to Cure Patients and Lessens the Risk of Recurrence



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.

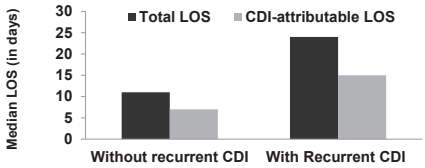
Recurrent CDI Is Costly: Healthcare Utilization for Recurrent CDI



*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



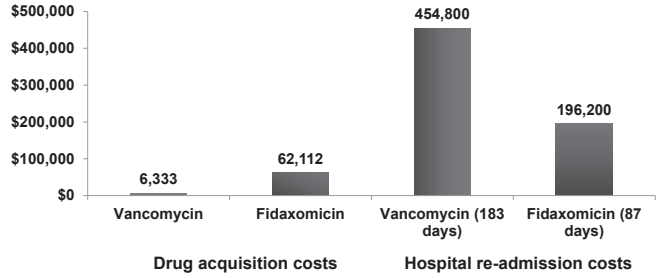
Cost in US dollars, median (IQR)	Without recurrent CDI	With recurrent CDI
CDI pharmacologic treatment	$60 (23 – 200)	$140 (30 – 260)
CDI-attributable hospitalization	$13,168 (7,525 – 24,455)	$28,218 (15,049 – 47,030)
Total hospitalization	$20,693 (11,287 – 41,386)	$45,148 (20, 693 – 82,772)

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.

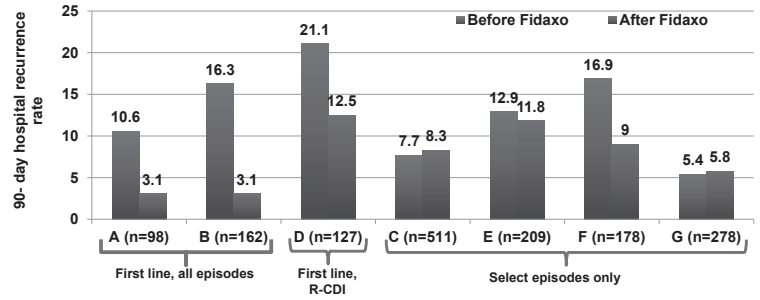
CDI-related re-admissions: fidaxomicin: 20.4%; vancomycin: 41.3%



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

Real-world Evidence That Fidaxomicin May Reduce These Costs?

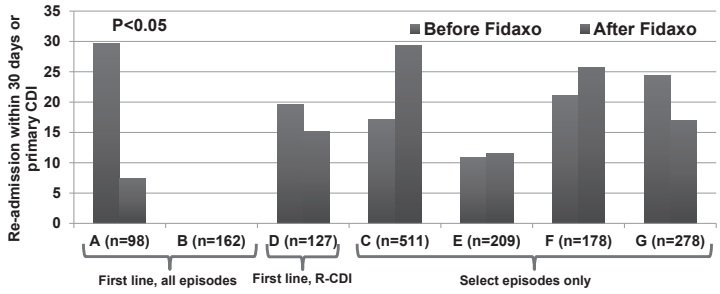
UK, 2012–13: Seven hospitals incorporate fidaxomicin into clinical protocols. Letters below indicate individual hospitals



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.

Recommendation for Recurrence of CDI in Adults

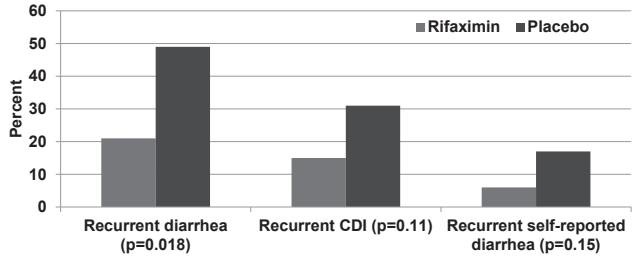
Clinical definition	Supportive clinical data	Recommended treatment
First recurrence		• VAN SD if metronidazole was used for the first episode OR • Prolonged tapered and pulsed VAN if VAN SD was used for first regimen OR • FDX SD if VAN was used for the initial episode
Second or subsequent recurrences		• VAN in a tapered or pulsed regimen OR • VAN SD followed by rifaximin 400 mg three times daily for 20 days OR • FDX SD OR • Fecal microbiota transplantation

VAN: vancomycin, FDX: fidaxomicin; SD: standard dose

McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.

Effect of Rifaximin to Prevent Recurrent Diarrhea

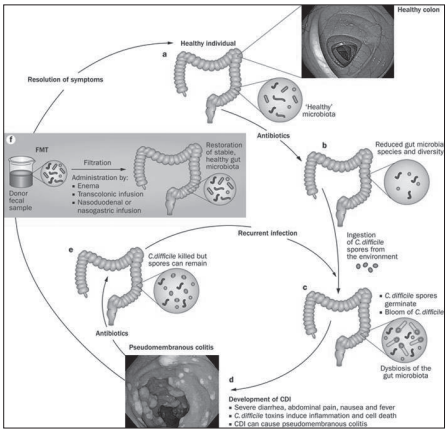
A Randomized Double-blind, Placebo-controlled Pilot Study to Assess the Effect of Rifaximin to Prevent Recurrent Diarrhea in 68 patients with *Clostridium difficile* Infection



Patients were given a 20-day course of rifaximin or matching placebo after completing a 10–14-day course of metronidazole or vancomycin therapy.

Garey K, et al. *J Antimicrob Chemother*. 2011;66:2850-5.

FMT for Patients with Recalcitrant CDI



Recurrent *C. difficile* Colitis

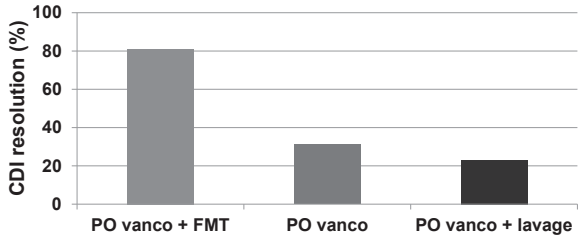
Case series involving 18 patients treated with donor stool administered via a nasogastric tube

	Before stool transplant	After stool transplant
Deaths	N/A	2 (unrelated)
# of Recurrence	64 (Range 2–7)	1

Aas J, et al. *Clin Infect Dis*. 2003;36:580-5.

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.

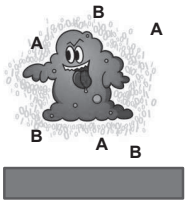
Protocol Utilizing a Staggered and Tapered Antibiotic Treatment Regimen for the Treatment of Recurrent CDI that has Failed to Respond to Standard Antibiotic Therapy

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

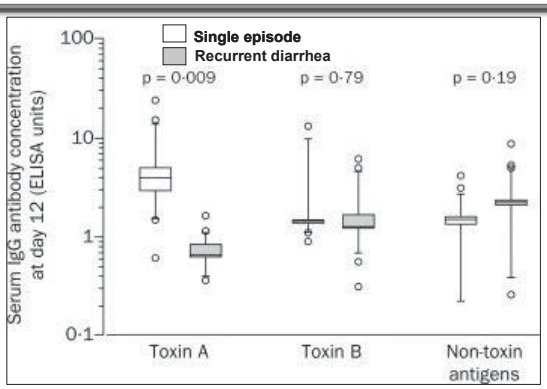
Bakken JS. *Clin Infect Dis*. 2014;59:858-61.

Explosion in Treatment Possibilities for CDI: Augment Immune Response!



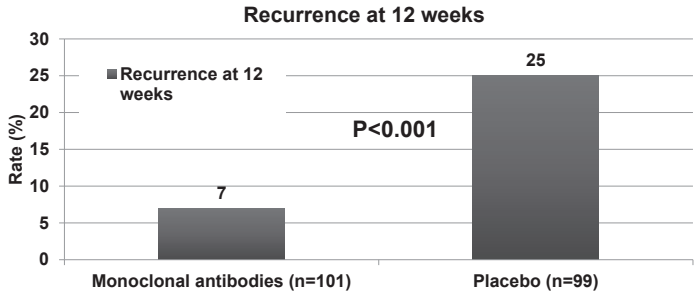
Current:	Probiotics FMT Use narrow-spectrum antibiotics	Vancomycin Fidaxomicin	IVIG **Monoclonal antibodies vs. *C. difficile* toxins**
Future:	2nd-generation FMT Non-tox *C. difficile* M3 Ecobiotics	Ridinilazole	Toxoid vaccines

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



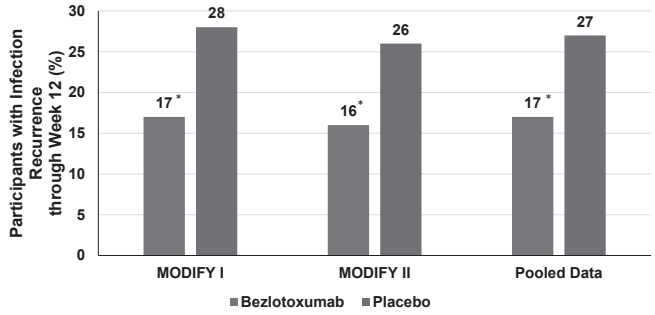
Kyne L, et al. *Lancet.* 2001;357:189-93.

Monoclonal Antibody: Phase II Study



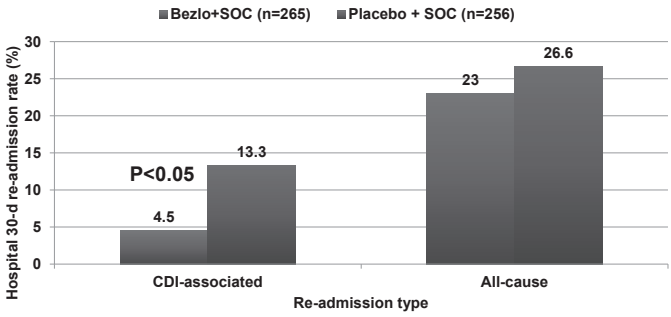
Lowy I, et al. *N Engl J Med.* 2010;362:197-205.

Phase III Studies of Bezlotoxumab: CDI Recurrence



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

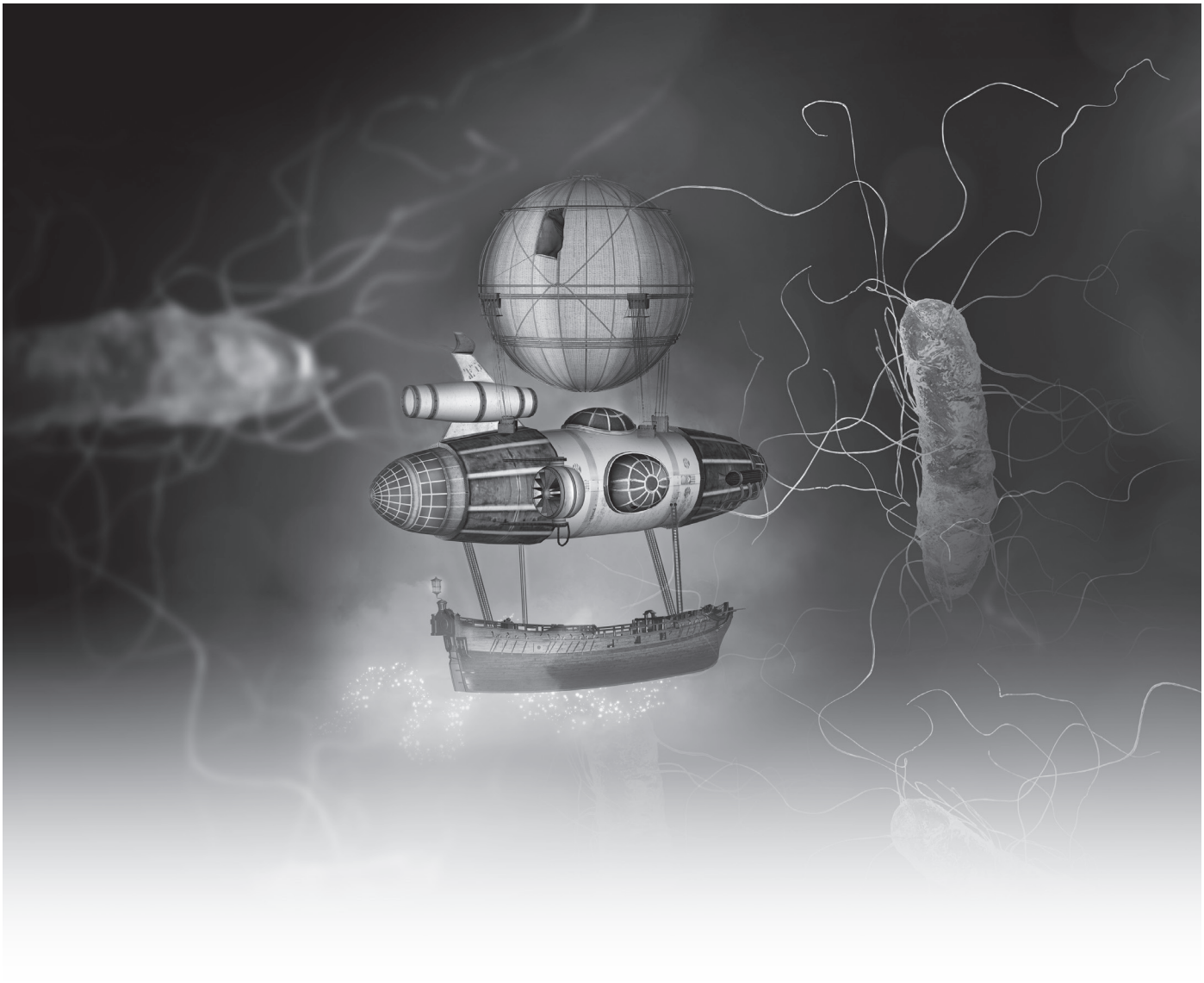
Bezlotoxumab Was Also Shown to Reduce Hospital Re-admissions (European Population)



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.

Final Conclusions

- Limit (eliminate) use of metronidazole
  - Pick a place for fidaxomicin
  - Be prepared for more competition in the narrow-spectrum anti-*C. difficile* world
- Immune response
  - Bezlotoxumab is here (and can be used in outpatient infusion centers)
- Complete the triad: Correct dysbiosis



MDR Gram-negative Bacteria: Practical Guidance on the Pathogen-specific Use of New Antimicrobials

George H. Karam, MD

Paula Garvey Manship Professor of Medicine
Department of Medicine
Louisiana State University School of Medicine in New Orleans
Baton Rouge Branch Campus
Baton Rouge, LA

CDC Antibiotic Resistance Threats in the US

CDC characterization of superbugs by threat levels

- Urgent
  - *Clostridium difficile*
  - Carbapenem-resistant Enterobacteriaceae (CRE)
  - Drug-resistant *Neisseria gonorrhoeae*
- Serious
- Concerning

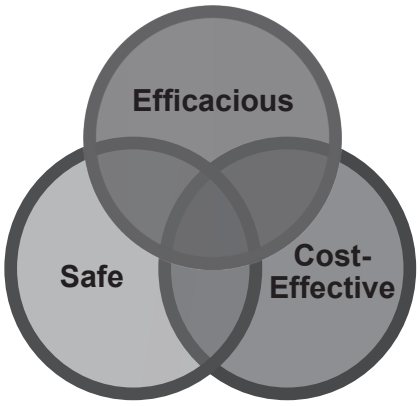
Centers for Disease Control. Available at: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.

WHO Antibiotic Resistant "Priority Pathogens" with "Critical" Need for R&D

- CR *Acinetobacter baumannii*
- CR *Pseudomonas aeruginosa*
- CR, ESBL-producing Enterobacteriaceae

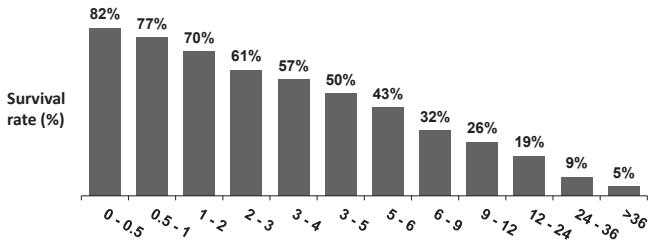
WHO, World Health Organization
R & D, Research and Development
CR, carbapenem-resistant
Tacconelli E, et al. *Lancet Infect Dis*. 2018;18:318-27.

Goals for Antimicrobial Therapy



Impact of Timing of Antimicrobial Agents on Survival in Sepsis

- Survival in 2,731 patients with septic shock[1]



Time To Appropriate Antimicrobial Therapy Following Onset of Hypotension (Hours)

Efficacious

- Retrospective analysis in 165 global ICUs with a total of 28,150 patients with severe sepsis or septic shock[2]
  - Survival benefit demonstrated with prompt antibiotics even in patients with only severe sepsis without shock
- Systematic review and meta-analysis questioning the above-stated benefits[3]

[1]Kumar A, et al. *Crit Care Med* 2006;34:1589-1596.; [2]Ferrer R, et al. *Crit Care Med* 2014;42:1749-1755.
[3]Sterling SA, et al. *Crit Care Med* 2015;43:1907-1915.

"Collateral" Effects of Antibiotic Use

- Collateral damage[1]
  - Described as the unanticipated consequences that may occur with antibiotics
- Collateral benefits[2]
  - Used to explain advantages that might be gained from antibiotics above that of antimicrobial killing

Safe

[1]Paterson DL. *Clin Infect Dis* 2004;38(Suppl 4):S341-345.
[2]Goldstein EJC. *Current Opin Infect Dis* 2011;24:S21-S31.

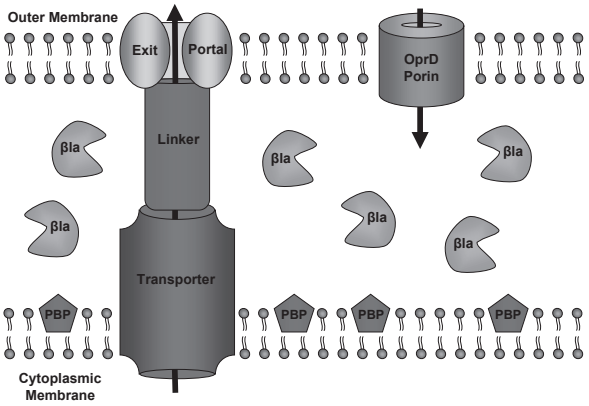
Medicare Spending Per Beneficiary (MSPB)

- **Definition of an MSPB episode**
  - Includes all services provided 3 days before the hospital admission through 30 days post-hospital discharge
- **Rationale for the 3-day-before-admission component**
  - To promote consistency between services, regardless of the diagnosis code and where services are provided
  - Allows diagnostic and non-diagnostic services related to the index submission to be captured in the inpatient payment
- **Rationale for the 30-days-after-discharge component**
  - Emphasizes the importance of care transition and care coordination in improving patient care

Cost-Effective

https://qualityreportingcenter.com/wp-content/uploads/2017/05/VBP-MSPB-Webinar-Transcript_05312017_vFINAL508.pdf

Classic Basis for Bacterial Resistance to β-Lactam Antibiotics



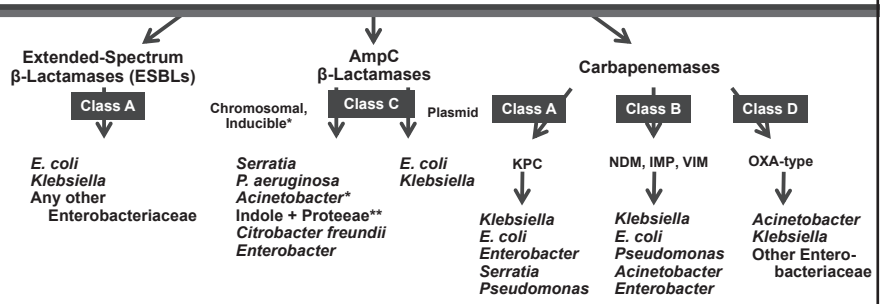
βla = β-lactamase PBP = Penicillin-binding protein

Mechanisms of Resistance in Antibiotic Classes Used To Treat Resistant Pathogens

	Permeability[5]	Enzymatic Destruction	Altered Binding Sites	Efflux[6]
β-lactams[1]	✓ (including porin channel closure with carbapenems)	β-lactamases	Penicillin-binding proteins	✓
Fluoroquinolones[2]	✓	Described, but not a classic resistance mechanism for quinolones[7]	• Alterations in DNA gyrase and Topoisomerase IV • Protection by plasmid-mediated qnr protein	✓
Aminoglycosides[3]	✓	Adenolating & acetylating enzymes	30S ribosomal subunit	✓
Tetracyclines[4]	✓	Modification enzymes	70S ribosomal subunit	✓

Adapted from Karam G, et al. *Crit Care.* 2016;20:136.
[1]Jacoby G. *N Engl J Med.* 2005;352:380-391.
[2]Jacoby G, Hooper DC, Jacoby GA. *Ann N Y Acad Sci.* 2015;1354:12-31.
[3]Mingeot-Leclercq MP, et al. *Antimicrob Agents Chemother.* 1999;43:727-37.
[4]Grossman TH, et al. *Antimicrob Agents Chemother.* 2012;56:2559-64.
[5]Delcour A. *Biochim Biophys Acta.* 2009;1794:808–816.
[6]Poole K. *J Antimicrob Chemother.* 2005;56:20–51.
[7]Jacoby GA. *Clin Infect Dis.* 2005;41:S120-S126.

A Clinical Approach To Gram-Negative Resistance Due To β-Lactamases✦



✦Based on the Ambler classification (Classes A, B, C, and D) of β-lactamases and using most likely pathogens (not at all-inclusive listing)
Serine-based β-lactamase = Classes A, B, and D Metallo-based β-lactamases = Class B KPC = *Klebsiella pneumoniae* carbapenemase
NDM = New Delhi metallo-β-lactamase IMP = imipenemase metallo-β-lactamase VIM = Verona integron-encoded OXA = oxacillinase

*AmpC β-lactamase of *Acinetobacter* is not inducible and, therefore, is less important for resistance in *Acinetobacter*.

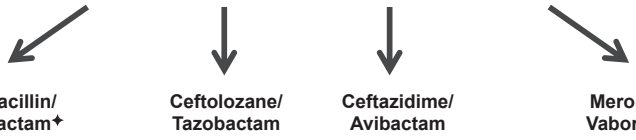
**The 3 genera comprising the Proteeae tribe of Enterobacteriaceae: *Proteus* (*P. mirabilis, P. vulgaris,* and *P. myxofaciens); Morganella* (*M. morganii*); and *Providencia* (*P. rettgeri, P. stuartii,* and *P. alcalifaciens).* Of these indole-positive organisms, *M. morganii, P. rettgeri,* and *P. stuartii* can produce inducible, chromosomal AmpC β-lactamase and have been described as causing systemic infections. (Kim B-N, et al. *Scand J Infect Dis* 2003;35:98-103)

Contemporary Issues Related to the Mechanisms By Which Clinically Important Resistance Occurs in Patients

- Acquisition of pathogens possessing resistance determinants
  - Travel
    - *J Antimicrob Chemother.* 2013;9:2144-2153.
  - Food
    - *Clin Infect Dis.* 2015;61:892-899.
  - Plasmid-mediated genetics
    - *Lancet Infect Dis.* 2016;16:161-168.
  - Transmissibility factors
    - *Clin Infect Dis.* 2018;66:489-493.
- Selection of resistant strains by antibiotic pressure
- Inadequate infection control

Evolution of Clinical Options

The Evolution of Clinical Options for β-Lactam/β-Lactamase Inhibitor Therapy



Piperacillin/ Tazobactam✦ | **Ceftolozane/ Tazobactam** | **Ceftazidime/ Avibactam** | **Meropenem/ Vaborbactam**

✦An old drug but new data about potential indications

The Concept of "Sparing"

- Carbapenem-sparing
- Pseudomonal-sparing
- Colistin-sparing

Potential Role for BLBLIs in Infections by ESBL-producing Organisms

- Multinational, retrospective cohort study by Gutiérrez-Gutiérrez et al showing that BLBLIs, if active *in vitro*, appear to be as effective as carbapenems for empirical and targeted bloodstream infections caused by ESBL-producing Enterobacteriaceae, regardless of source and specific species, if used at appropriate doses
  - ***Antimicrob Agents Chemother.* 2016;60:4159–4169.**
- Suggestion by Bassetti et al that the best alternative to carbapenems for the treatment of ESBL infections may be by BLBLIs, mainly piperacillin–tazobactam, if the MIC of the ESBL-producing pathogen is ≤16/4 μg/mL
  - ***Curr Opin Infect Dis.* 2016;29:583–594.**
- Perspective paper suggesting potential roles for β-lactamase inhibitor combinations in treatment of ESBL infections (***Lancet Infect Dis.* 2015;15:475-485.)**
  - Infections of the urinary tract
  - Non-urinary infections with isolates having low MICs
  - Clinical infections in which source control has been achieved

BLBLIs, β-lactam/β-lactamase inhibitors
BSIs, bloodstream infections

Harris *et al. Trials* (2015) 16:24
DOI 10.1186/s13063-014-0541-9

TRIALS

STUDY PROTOCOL **Open Access**

Meropenem versus piperacillin-tazobactam for definitive treatment of bloodstream infections due to ceftriaxone non-susceptible *Escherichia coli* and *Klebsiella* spp (the MERINO trial): study protocol for a randomised controlled trial

Patrick NA Harris[1*], Anton Y Peleg[2], Jon Iredell[3], Paul R Ingram[4,5], Spiros Miyakis[6], Andrew J Stewardson[7], Benjamin A Rogers[8], Emma S McBryde[9], Jason A Roberts[10], Jeff Lipman[10], Eugene Athan[11], Sanjoy K Paul[12], Peter Baker[13], Tiffany Harris-Brown[1] and David L Paterson[1]

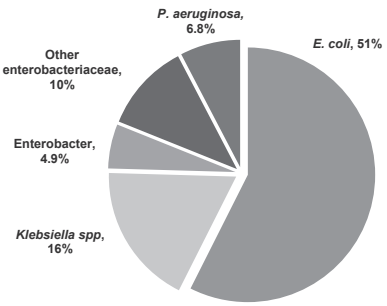
ClinicalTrials.gov Identifier: NCT02176122

Recruitment Status ⓘ : Terminated (Secondary to third interim analysis by the study DSMB.)
First Posted ⓘ : June 26, 2014
Last Update Posted ⓘ : November 27, 2017

Pinned Tweet

MERINO Trial @MerinoTrial · Mar 17
We will be presenting the headline @MerinoTrial results in late breaker clinical trials session @ECCMID in Madrid - looking forward to sharing the results after years of hard work from many investigators in 9 countries @UQMedicine @UQ_News @ASIDANZ @davidantibiotic @padstamundo

Predictors of *Pseudomonas aeruginosa* Bacteremia



- **4114 Gram-negative bacteremia isolates:**
  - ***P. aeruginosa* 1:2,000 admissions**

Schechner V, et al. *Clin Infect Dis.* 2009;48:580-586.

Table 2. Independent predictors of *Pseudomonas aeruginosa* bacteremia upon hospital admission among patients without severe immunodeficiency on the basis of multivariate logistic regression analysis.

Variable	OR (95% CI)	*P*
Presence of a urinary device[a]	6.80 (2.53–18.26)	<.001
Age >90 years	5.39 (1.91–15.17)	.001
Recent antimicrobial use[b]	3.70 (1.87–7.36)	<.001
Presence of a central venous catheter	2.97 (1.31–6.73)	.009

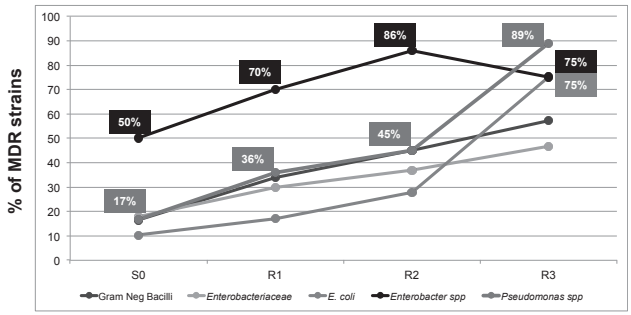
Table 3. Risk classification for *Pseudomonas aeruginosa* bacteremia among 250 patients without severe immunodeficiency, according to the total number of independent predictors, and the number of patients needed to treat in each group to effectively treat a single case of *P. aeruginosa* bacteremia.

No. of predictors (risk category)	Occurrence based on data, %	Probability of *P. aeruginosa* bacteremia, %	No. of patients needed to treat		
			Per risk group[a]	For risk group or higher risk[b]	For risk group or lower risk[c]
0	71.77	2.36	42.4	20.00	42.4
1	24.39	8.84	11.3	8.55	25.0
2	3.75	28.13	3.55	3.35	20.4
3	0.09	100.00	1.00	1.00	20
4	0.00	…	…	…	…

[a] For treatment of only patients with gram-negative bacteremia in the specific risk category.
[b] For treatment of all patients with gram-negative bacteremia in the specific risk category or higher.
[c] For treatment of all patients with gram-negative bacteremia in the specific risk category or lower. This provides an estimate of limiting the overuse of anti-pseudomonal agents per 1 missed case of *P. aeruginosa* bacteremia.

Increased Risk of Resistant Gram-negative Bacilli in Late Nosocomial Infections

- 98 ICU patients who underwent repeated surgery for persistent peritonitis
- Culture of peritoneal fluid at each reoperation
- Analysis of emergence of MDR organisms in surgical samples



S0: Index operation **R1: First reoperation** **R2: Second reoperation** **R3: Third reoperation**

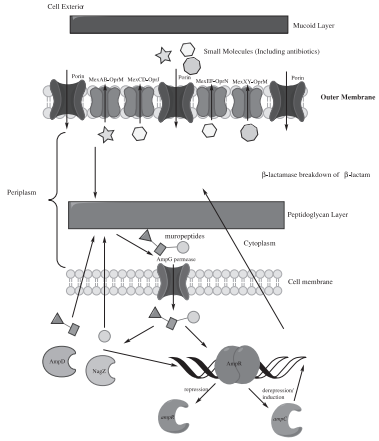
Montravers P, et al. *Crit Care.* 2015;19:70.

Multidrug-Resistant *P. aeruginosa* Linked to Overuse of Traditional Antibiotics with Antipseudomonal Activity

- In a 2-year case-control study of patients (N=2613) admitted to 3 ICUs in a large teaching hospital in Paris, France
  - Prolonged receipt of antibiotics with specific antipseudomonal activity (most notably ciprofloxacin) associated with the emergence of multidrug-resistant *P. aeruginosa*
  - Interpretation of the data: "if treatment with an antibiotic active against Gram-negative bacteria is needed, agents with little antipseudomonal activity should be preferred over those with specific antipseudomonal activity to limit the emergence of MDRPA (multidrug-resistant *P. aeruginosa*)."

Paramythiotou E, et al. *Clin Infect Dis.* 2004;38:670–677.

Resistance Mechanisms in *Pseudomonas aeruginosa*



- **Mucoid layer**
  - Mucoid layer with increased thickness outside the outer membrane
- **Outer membrane porins**
  - Loss of porins
- **Efflux pumps**
  - Efflux pumps in the outer membrane; when present, ability to pump antibiotics out the cell
- **PBP alterations**
  - Located in the peptidoglycan layer; altered to prevent interaction of antibiotics with their targets
- **β-lactamase upregulation**
  - Regulation of chromosomal AmpC, which involves a complex relationship between peptidoglycan breakdown, β-lactam exposure, and gene regulation leading to overexpression of the AmpC enzyme
  - Location of β-lactamases in periplasmic space with the ability to break down β-lactam antibiotics and/or β-lactamase inhibitors

Winkler ML, et al. *Antimicrob Agents Chemother.* 2015;59:1020-1029.

Resistance in *Pseudomonas aeruginosa*

- Resistance mechanisms regulated by genetic operons on the chromosome of *P. aeruginosa*
  - Outer membrane porins (carbapenems)
  - Efflux pumps (fluoroquinolones; meropenem)
  - AmpC β-lactamases (non-carbapenem β-lactams)

Lister PD, Wolter DJ. *Clin Infect Dis.* 2005;40:S105-S114.
Quale J, et al. *Antimicrob Agents Chemother.* 2006;50:1633-1641.

Efflux Pumps in *Pseudomonas aeruginosa*: Agents Subject To Extrusion By These Pumps

MexAB-OprM*	MexCD-OprJ	MexEF-OprN	MexXY-OprM
Fluoroquinolones	Fluoroquinolones	Fluoroquinolones	Fluoroquinolones
Tetracycline	Piperacillin	Trimethoprim	Aminoglycosides
Chloramphenicol	Cefepime	Chloramphenicol	Piperacillin
Piperacillin	Meropenem		Cefepime
Cefepime			Meropenem
Aztreonam			Tigecycline‡
Meropenem			
Doripenem**			

*Constitutively expressed in virtually all isolates
Quale J, et al. *Antimicrob Agents Chemother.* 2006;50:1633-1641.
**Dalhoff A, et al. *Biochem Pharmacol.* 2006;71:1085-1095.
‡Dean CR, et al. *Antimicrob Agents Chemother.* 2003;47:972-978.

Mechanisms Contributing to the Expression of Carbapenem Resistance in *P. aeruginosa*

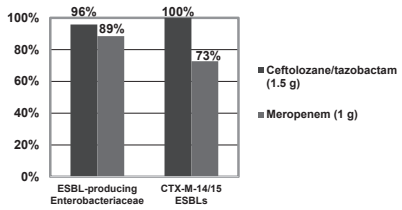
- Selection by carbapenems of porin-deficient mutants
- Selection by fluoroquinolones of *mex*EF-*opr*N-overexpressing mutant strains of *Pseudomonas aeruginosa* with
  (1) upregulated efflux pumps
  (2) closed porin channels

Lister PD, Wolter DJ. *Clin Infect Dis.* 2005;40:S105-S114.
Livermore DM. *Clin Infect Dis.* 2002;34:634-640.

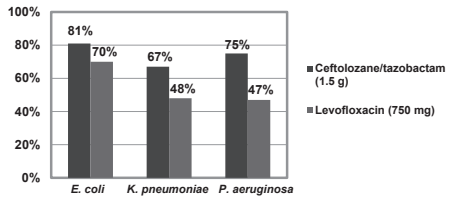
Ceftolozane/Tazobactam

- Novel cephalosporin in combination with a β-lactamase inhibitor with broad-spectrum activity
  - Ceftolozane stable in the presence of the 3 chromosomal mechanisms of resistance in *P. aeruginosa*

Clinical Cure Rates per Pathogen (cIAI)1



Clinical Cure Rates per Pathogen (cUTI)2



[1]Solomkin J, et al. *Clin Infect Dis.* 2015;60:1462-1471.
[2]Wagenlehner FM, et al. *Lancet* 2015;385:1949-1956.

Treatment for Resistant *Pseudomonas aeruginosa*

- Comparison of *in vitro* inhibitory activity of ceftazidime/avibactam and ceftolozane/tazobactam against 290 meropenem-nonsusceptible *Pseudomonas aeruginosa* non-duplicate clinical isolates from 34 U.S. hospitals
- Significantly higher inhibitory activity of ceftolozane/tazobactam versus ceftazidime/avibactam
  - Height of inhibitory activity of ceftolozane/tazobactam sustained when the site of origin (respiratory, blood, or wound) and nonsusceptibility to other β-lactam antimicrobials considered
- Exclusive presence of the VIM metallo-β-lactamase among only 4% of the subset of isolates nonsusceptible to ceftazidime/avibactam, ceftolozane/tazobactam, or both
- Conclusion: "These findings suggest an important role for both ceftazidime/avibactam and ceftolozane/tazobactam against carbapenem-nonsusceptible *Pseudomonas aeruginosa*."

Grupper M, et al. *Antimicrob Agents Chemother.* 2017;61:e00875-17.

A Concept Map for Considering Carbapenem Resistance

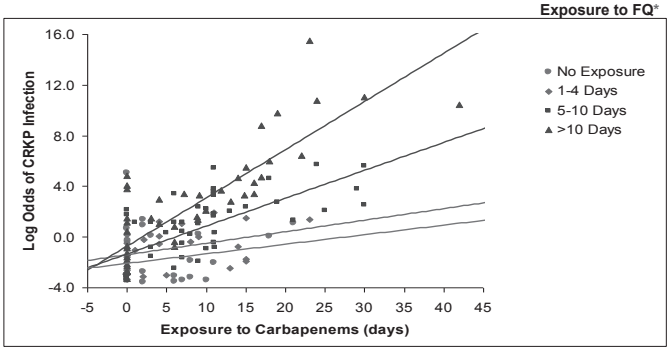
Carbapenemase production

- **Class A β-lactamases (e.g., KPCs)**
- **Class B β-lactamases (e.g., NDMs, VIMs, IMPs)**
- **Class D β-lactamases (e.g., OXAs)**

No carbapenemase production

- **Porin channel closure**
- **Efflux**
- **β-lactamases other than carbapenemases (Class C)**

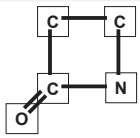
Antibiotic Use and the Risk of Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP)



*FQ, Fluoroquinolones

Kritsotakis EI, et al. *J Antimicrob Chemother.* 2011;66:1383-1391.

β-Lactamase Inhibitors



β-Lactams

- Sulbactam
- Clavulanate
- Tazobactam

Non-β-Lactams

- Avibactam
- Vaborbactam
- Relebactam
- ME1071

Activity of β-lactamase Inhibitors Against β-lactamases

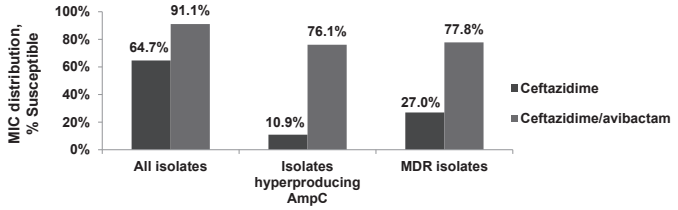
Spectrum	β-lactamase Inhibitor			
	Tazobactam	Avibactam	Vaborbactam	Relebactam
Class A narrow-spectrum	+	+	+	+
Class A ESBLs	+	+	+	+
Class A carbapenemases (KPC)		+	+	+
Class B metallo-β-lactamases				
Some class C enzymes	+/-	+	+	+
Some class D enzymes		+		

Drawz SM, Bonomo RA. *Clin Microbiol Rev.* 2010;14:160-201.

Toussaint KA, Gallagher JC. *Ann Pharmacother.* 2015;49:86-98.

Ceftazidime/Avibactam

- 3rd-generation cephalosporin and non-β-lactam β-lactamase inhibitor
- Broad-spectrum activity[1]
  - Most ESBLs
  - KPCs
  - *P. aeruginosa* in presence of some AmpC β-lactamases and certain strains lacking OprD
- Changes in *P. aeruginosa* susceptibility with addition of avibactam



Torrens G, et al. *Antimicrob Agents Chemother.* 2016;60:6407-6410.

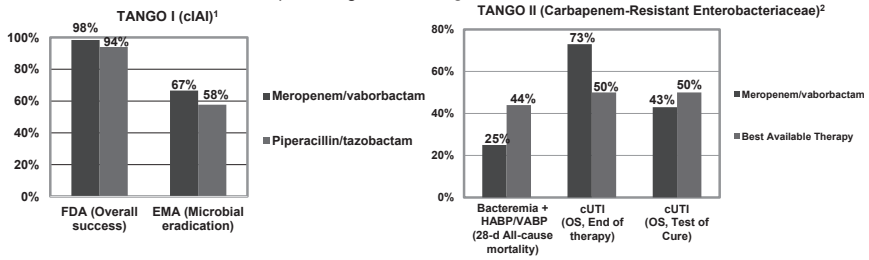
Ceftazidime/Avibactam
Emergence of Resistance Among Enterobacteriaceae

- 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 *Klebsiella 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. *Antimicrob Agents Chemother.* 2015;59: 6605-6607.
[2]Nelson K et al. *Antimicrob Agents Chemother* 2017;61(10):e00989-17.
[3]Shields RK, et al. *Clin Infect Dis.* 2016; 63:1615-1618.
[4]Shields RK, et al. *Antimicrob Agents Chemother.* 2017;61(3): e02097-16.
[5]Castanheira M, et al. *Antimicrob Agents Chemother.* 2017;61(3): e01369-16.
[6]Spellberg B, Bonomo RA. *Clin Infect Dis.* 2016;63:1619-1621.

Meropenem/Vaborbactam

- Vaborbactam (previously RPX7009)
  - Unique boronic acid non-suicidal β-lactamase inhibitor
  - Potent inhibitor of KPCs
  - Minimal effect for meropenem against *P. aeruginosa*



[1]Kaye KS, et al. *JAMA.* 2018;319:788-799.
[2]Wunderink R, et al. *Open Forum Infect Dis.* 2017;4(Suppl 1):S536-S537.

HABP, Hospital-acquired bacterial pneumonia
VABP, Ventilator-acquired bacterial pneumonia
OS, Overall success

In Vitro Activity of Carbapenem/β-lactamase-inhibitor Combinations Against *Pseudomonas aeruginosa*

4,500 isolates from 11 hospitals in Brooklyn and Queens, NY: Nov 2013 to Jan 2014[1]

Species (n)	Meropenem		Meropenem/Vaborbactam	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Klebsiella pneumoniae (KPC+) (121)	8	64	0.03 / 8	0.5 / 8
Pseudomonas aeruginosa (96)	8	32	8 / 8	32 / 8
Acinetobacter baumannii (98)	32	64	32 / 8	64 / 8

4,000 isolates from 11 hospitals in Brooklyn and Queens, NY: Nov 2013 to Jan 2014[2]

Species (n)	Imipenem		Imipenem/Relebactam	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
bla_{KPC}-possessing *K. pneumoniae* (111)	16	>16	0.25 / 4	1 / 4
Pseudomonas aeruginosa (490)	2	16	0.5 /4	2 /4
Imipenem-resistant *P. aeruginosa* (144)	8	>16	1 /4	2 /4

MIC values in µg/mL

[1]Lapuebla A, et al. *Antimicrob Agents Chemother.* 2015;59:4856-4860.
[2]Lapuebla A, et al. *Antimicrob Agents Chemother.* 2015;59:5029-5031.

The Clinical Response of "Colistin-Sparing"

(facilitated by data suggesting that newer agents might be better for CRE infections)

- Ceftazidime/avibactam
  - Higher rates of clinical success (*P*=0.006) and survival (*P*=0.01) and less nephrotoxicity than aminoglycoside- and colistin-containing regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia[1]
  - 23% reduced risk for death and 64% probability of better outcome compared to colistin for carbapenem-resistant Enterobacteriaceae (CRE)[2]
- Meropenem/vaborbactam[3]
  - TANGO-2, comparing meropenem/vaborbactam monotherapy to best available therapy in serious infections due to carbapenem-resistant Enterobacteriaceae (CRE)
    - Lower mortality and renal toxicity
- Plazomicin[4]
  - CARE Study, comparing plazomicin versus colistin combined with meropenem or tigecycline in patients with infections due to carbapenem-resistant Enterobacteriaceae (CRE)
    - 70.5% relative reduction in all-cause mortality

[1]Shields RK, et al. *Antimicrob Agents Chemother.* 2017;61:e00883-17.
[2]van Duin D, et al. *Clin Infect Dis.* 2018;66:163-171.
[3]Wunderink R, et al. 2nd ASM-Microbe Meeting 2017, New Orleans, Louisiana. Abstract 1867.
[4]Connolly L, et al. 27th ECCMID 2017, Vienna. Abstract OS0250F.

Clinical Summary of Data About β-lactam/β-lactamase Inhibitor Therapy in the ICU

Piperacillin/ Tazobactam✦	Ceftolozane/ Tazobactam	Ceftazidime/ Avibactam	Meropenem/ Vaborbactam
• Potential role for ESBLs being determined by MERINO trial • Lack of efficacy by tazobactam in improving *P. aeruginosa* activity of piperacillin • Recent data about nephrotoxicity*	• Most active agent against *P. aeruginosa*	• Active against KPC-producing organisms • Pneumonia indication	• Active against KPC-producing organisms • Lack of efficacy by vaborbactam in improving susceptibility against meropenem-resistant *P. aeruginosa*

✦D'Angelo RG, et al. *Expert Opin Pharmacother.* 2016;17:953-967.
✦Bassetti M, et al. *Curr Opinion Infect Dis.* 2016;29:583-594.
*Hammond DA, et al. *Clin Infect Dis.* 2017;64:666–674.

Stratification Based on Risk of Resistance

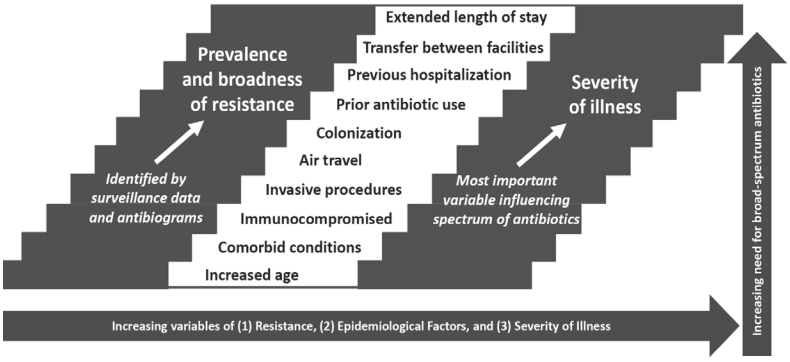
Risk factors for ESBL+ Enterobactericeae[1]	OR (95% CI)	*P* value
Recent hospitalization in past 12 months	5.69 (2.94–10.99)	0.001
Admission from another health care facility	5.61 (1.65–19.08)	0.006
Charlson comorbidity index > 4	3.80 (1.90–7.59)	0.001
Previous therapy with β-lactams and/or quinolones	3.68 (1.96–6.91)	0.001
History of urinary catheterization in past 30 days	3.52 (1.96–6.91)	0.001
Age >70 years	3.20 (1.79–5.70)	0.001

Patient Characteristics for Resistance in *P. aeruginosa* bacteremia (PAB)[2]	MDR PAB n = 127	Non-MDR PAB n = 582	*P* value
Nosocomial infection (%)	85	68	<0.0001
Longer hospital stay (mean days)	31.83	16.38	<0.0001
Prior antibiotic therapy (%)	85.8	53.4	<0.0001
Prior steroid therapy (%)	41.7	33.8	0.03
Bladder catheter (%)	53.5	37.5	<0.0001
Inappropriate empirical antibiotic (%)	62.2	27	<0.0001

Multivariate Analysis of Risk Factors for Isolation Carbapenem-resistant Enterobacteriaceae (CRE)[3]	Adjusted odds ratio	95% Confidence Interval	*P* value
Weighted index comorbidity >3	4.85	1.63–14.41	0.004
Immune suppression	3.92	1.08–14.28	0.038
Indwelling devices	5.21	1.09–24.96	0.39
Any antibiotic exposure	3.89	0.71–21.46	0.119

[1]Tumbarello M, et al. *Antimicrob Agents Chemother.* 2011;55:3485–3490.
[2]Morata L, et al. *Antimicrob Agents Chemother.* 2012;56:4833-4837.
[3]Bhargava A, et al. *Infect Control Hosp Epidemiol.* 2014;35:398-405.

Variables Influencing Patient Stratification for Empiric Antibiotic Therapy

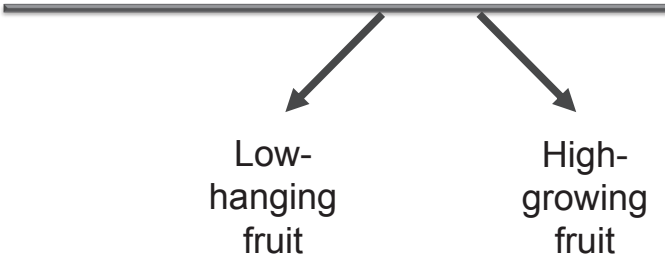


Karam G, et al. *Crit Care.* 2016;20:136.

Evolution of What Defines "Low-Hanging Fruit" Projects in Antimicrobial Stewardship

- Goff DA, et al. *Clin Infect Dis.* 2012;55:587-592.
  - Intravenous-to-oral conversions
  - Batching of intravenous antimicrobials
  - Therapeutic substitutions
  - Formulary restriction
- Brink A, van den Berg D. University of Dundee and British Society of Antimicrobial Chemotherapy https://www.futurelearn.com/courses/antimicrobial-stewardship/0/steps/7579
  - Obtaining cultures prior to antibiotic prescription
  - Concurrent use of ≥4 antibiotics
  - Duration of antibiotic therapy
    - >7 days
    - >14 days
  - Concurrent "double coverage"
    - Redundant anaerobic coverage
    - Excess days of empiric Gram-positive and Gram-negative coverage (e.g., HAP)

A Philosophical Approach to Antimicrobial Stewardship



A Concept Map for Fundamental Forms of Gram-negative Antimicrobial Therapy