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The Great ID Debates of One-Eight

	twitter
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Disclosures

- **Monica V. Mahoney:** CutisPharma: Advisory Board; Melinta Therapeutics: Advisory Board; Roche Diagnostics: Advisory Board; Tetraphase Pharmaceuticals, Inc.: Advisory Board
- All other planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

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Vancomycin vs Linezolid for Empiric Coverage of MRSA in Nosocomial Pneumonia

Vancomycin **Brandon Dionne** @BWDionne

Linezolid **Meghan N. Jeffres** @PharmerMeg

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Audience Poll

In a patient with nosocomial (HAP/VAP) pneumonia, which medication should be used first line as empiric therapy?

A. Vancomycin
B. Linezolid

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Empiric Anti-MRSA Agent: Vancomycin

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MRSA in Nosocomial Pneumonia

- *Staphylococcus aureus* was responsible for 31.9-36.5% of HAP/VAP in SENTRY surveillance program
  - ~50% were methicillin-resistant

- MRSA colonization
  - MRSA nasal swabs have 99% negative predictive value for MRSA pneumonia
  - Positive predictive value only around 37%

Jones RN. Clin Infect Dis. 2010;51(Suppl 1):S81–S87.
Smith MN, et al. *J Crit Care*. 2017;38:168-171.

2016 IDSA/ATS HAP/VAP Guidelines

- Recommend vancomycin or linezolid if:
  - Previous IV antibiotics within 90 days
  - Septic shock or ventilatory support required due to pneumonia
  - MRSA prevalence >10-20% in unit/institution
  - ARDS preceding VAP
  - Acute renal replacement therapy preceding VAP

- Recommended duration of 7 days

Kalil AC, et al. *Clin Infect Dis*. 2016;63(5):e61-e111.

Vancomycin vs Linezolid Pneumonia RCTs

	Rubinstein et al.			Wunderink et al.		
	Vancomycin	Linezolid	p-value	Vancomycin	Linezolid	p-value
Clinical Cure	68.1%	66.4%	0.79	64.9%	67.9%	0.57
Microbiologic Cure	71.8%	67.9%	0.69	53.2%	61.8%	0.27
Adverse Events	33.7%	31.0%	--	14.0%	14.0%	--
Conclusion	Linezolid non-inferior to vancomycin			Linezolid non-inferior to vancomycin		

Rubinstein E, et al. Clin Infect Dis. 2001;32(3):402-12.
Wunderink R, et al. Clin Ther. 2003;25(3):980-92.

Vancomycin vs. Linezolid Meta-analysis

- Includes 9 randomized trials with direct comparison in nosocomial pneumonia
- 99.9% power to detect a difference in clinical cure and mortality
- Most trials used a fixed dose of vancomycin 1 g IV q12h
- Many did not allow monitoring and dose adjustment of vancomycin

Kalil AC, et al. *BMJ Open*. 2013;3(10):e003912.

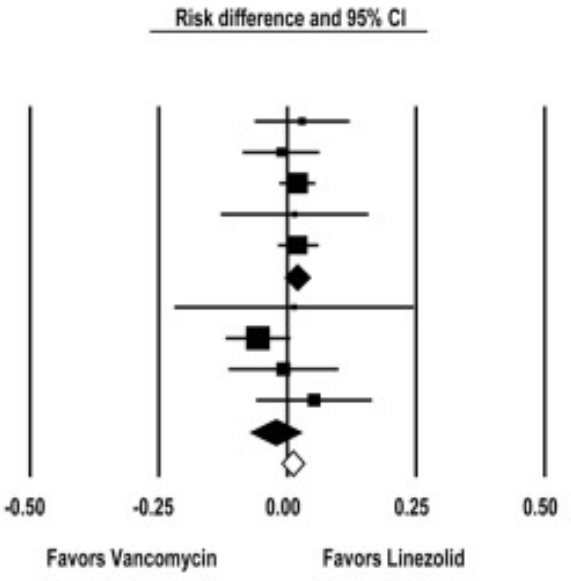
Vancomycin Dosing in RCTs

	Starting Dose of Vancomycin	Adjustment allowed
Rubinstein (2001)	1 g q12h	? (for renal function)
Stevens (2002)	1 g q12h	X
Kaplan (2003)	10-15 mg/kg q6-24h (pediatric)	X
Wunderink (2003)	1 g q12h	X
Jaksic (2006)	1 g q12h	✔ (no details)
Kohno (2007)	1 g q12h	✔ (no details)
Wunderink (2008)	1 g q12h	X
Lin (2008)	1 g or 750 mg (>60 yo) q12h	X
Wunderink (2012)	15 mg/kg q12h	✔

Meta-analysis – Clinical Cure

(a) **Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Clinical Response***

Group by Study Design	Study name	Statistics for each study				Mortality / Total	
		Risk difference	Lower limit	Upper limit	p-Value	Linezolid	Vancomycin
Randomized Double-blind	Rubinstein E 2001	0.029	-0.064	0.121	0.548	71 / 203	62 / 193
Randomized Double-blind	Wunderink R 2003	-0.012	-0.088	0.063	0.747	114 / 321	111 / 302
Randomized Double-blind	Jaksic B 2006	0.019	-0.016	0.055	0.288	19 / 304	13 / 301
Randomized Double-blind	Lin D 2008	0.014	-0.130	0.158	0.848	19 / 71	18 / 71
Randomized Double-blind	Wunderink R 2012	0.021	-0.019	0.062	0.306	95 / 597	81 / 587
Randomized Double-blind		0.017	-0.007	0.041	0.159	318 / 1496	285 / 1454
Randomized Open-label	Stevens D 2002	0.013	-0.221	0.247	0.914	20 / 39	16 / 32
Randomized Open-label	Kaplan S 2003	-0.057	-0.121	0.007	0.081	9 / 215	10 / 101
Randomized Open-label	Kohno S 2007	-0.008	-0.115	0.100	0.889	11 / 100	6 / 51
Randomized Open-label	Wunderink R 2008	0.052	-0.062	0.165	0.372	13 / 75	9 / 74
Randomized Open-label		-0.024	-0.073	0.024	0.327	53 / 429	41 / 258
Overall		0.009	-0.012	0.031	0.409	371 / 1925	326 / 1712



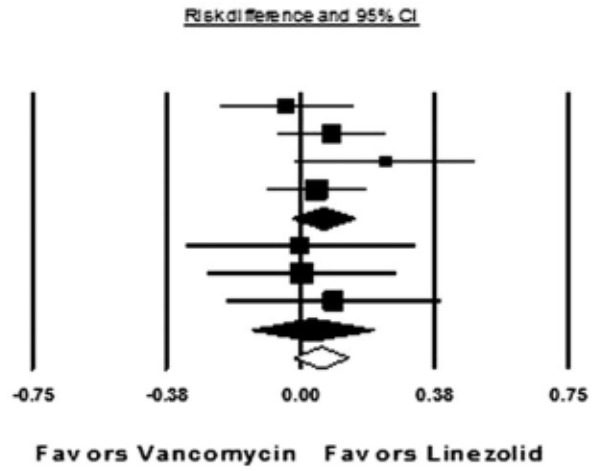
*Intention-to-Treat Population. Z=0.826; P=0.409; Heterogeneity: Q=5.878; P=0.661; I2=0%

Kalil AC, et al. *BMJ Open*. 2013;3(10):e003912.

Meta-analysis – Microbiologic Cure

(a) **Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Microbiological Eradication***

Group by Study Design	Study name	Statistics for each study: Risk difference	Lower limit	Upper limit	p-Value	Micro Eradication / Total: Linezolid	Vancomycin
Randomized Double-blind	Rubinstein E 2001	-0.039	-0.228	0.150	0.688	36 / 53	28 / 39
Randomized Double-blind	Wunderink R 2003	0.087	-0.068	0.242	0.273	47 / 76	42 / 79
Randomized Double-blind	Lin D 2008	0.237	-0.018	0.492	0.068	17 / 22	15 / 28
Randomized Double-blind	Wunderink R 2012	0.044	-0.095	0.183	0.537	35 / 97	26 / 82
Randomized Double-blind		0.062	-0.025	0.149	0.161	135 / 248	111 / 228
Randomized Open-label	Stevens D 2002	0.000	-0.324	0.324	1.000	9 / 12	12 / 16
Randomized Open-label	Kohno S 2007	0.003	-0.267	0.273	0.983	13 / 35	7 / 19
Randomized Open-label	Wunderink R 2008	0.092	-0.211	0.394	0.553	13 / 23	9 / 19
Randomized Open-label		0.030	-0.140	0.201	0.727	35 / 70	28 / 54
Overall		0.056	-0.022	0.133	0.159	170 / 318	139 / 282



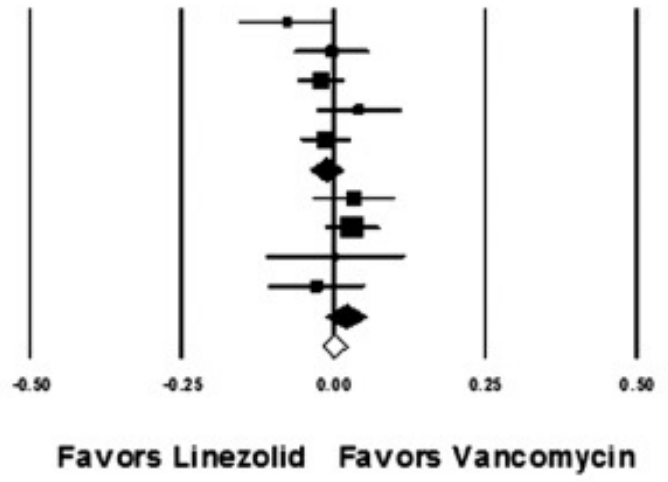
*Microbiological Evaluable/Per-Protocol Population. Z=1.408; P=0.159; Heterogeneity: Q=3.404; P=0.757; I2=0%

Kalil AC, et al. *BMJ Open*. 2013;3(10):e003912.

Meta-analysis – Mortality

Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Mortality*

Group by Study Design	Study name	Risk difference	Lower limit	Upper limit	p-Value	Mortality / Total: Linezolid	Mortality / Total: Vancomycin
Randomized Double-blind	Rubinstein E 2001	-0.077	-0.157	0.004	0.063	36 / 203	49 / 193
Randomized Double-blind	Wunderink R 2003	-0.003	-0.066	0.060	0.935	64 / 321	61 / 302
Randomized Double-blind	Jaksic B 2006	-0.020	-0.060	0.019	0.310	17 / 304	23 / 301
Randomized Double-blind	Lin D 2008	0.042	-0.029	0.113	0.243	5 / 71	2 / 71
Randomized Double-blind	Wunderink R 2012	-0.013	-0.055	0.029	0.549	94 / 597	100 / 587
Randomized Double-blind		-0.013	-0.040	0.014	0.342	216 / 1496	235 / 1454
Randomized Open-label	Stevens D 2002	0.033	-0.035	0.101	0.337	44 / 240	33 / 220
Randomized Open-label	Kaplan S 2003	0.031	-0.015	0.077	0.189	13 / 215	3 / 101
Randomized Open-label	Kohno S 2007	0.003	-0.114	0.119	0.963	14 / 100	7 / 51
Randomized Open-label	Wunderink R 2008	-0.028	-0.108	0.053	0.498	4 / 75	6 / 74
Randomized Open-label		0.019	-0.014	0.052	0.253	75 / 630	49 / 446
Overall		-0.000	-0.021	0.021	0.992	291 / 2126	284 / 1900



*Intention-to-Treat Population. Z=0.010; P=0.992; Heterogeneity: Q=9.251; P=0.322; I2=13.5%

Kalil AC, et al. *BMJ Open*. 2013;3(10):e003912.

Problems with Linezolid

- Outbreaks of linezolid-resistant *S. aureus* have been reported
- Higher drug costs
- Drug interactions
- Bacteriostatic
- Adverse effects

Sánchez García M, et al. *JAMA*. 2010;303(22):2260-4.

Linezolid Adverse Effects

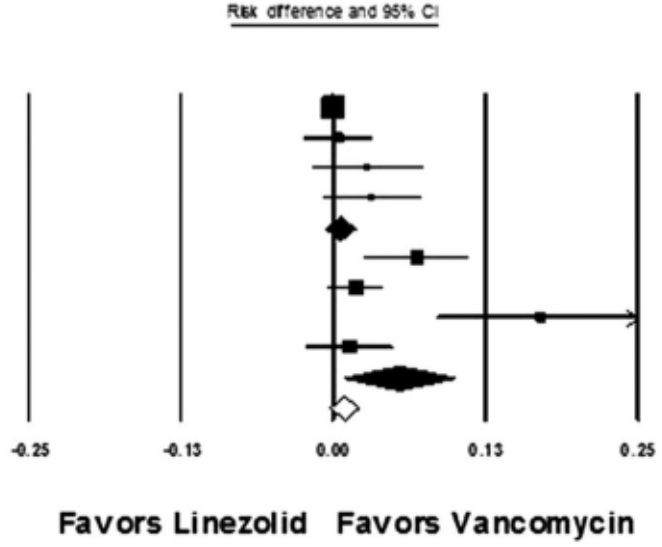
- Neurotoxicity - peripheral neuropathy is potentially irreversible
- Serotonin syndrome
- Gastrointestinal symptoms - higher incidence in linezolid group in the meta-analysis
- Thrombocytopenia

Kalil AC, et al. *BMJ Open*. 2013;3(10):e003912.

Meta-analysis – Thrombocytopenia

(b) **Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Thrombocytopenia***

Group by Study Design	Study name	Statistics for each study: Risk difference	Lower limit	Upper limit	p-Value	Thrombocytopenia / Total: Linezolid	Vancomycin
Randomized Double-blind	Rubinstein E 2001	0.000	-0.010	0.010	1.000	0 / 203	0 / 193
Randomized Double-blind	Wunderink R 2003	0.004	-0.025	0.033	0.772	12 / 321	10 / 302
Randomized Double-blind	Lin 2008	0.028	-0.018	0.075	0.234	2 / 71	0 / 71
Randomized Double-blind	Wunderink 2012	0.032	-0.008	0.072	0.122	97 / 597	77 / 587
Randomized Double-blind		0.005	-0.007	0.017	0.403	111 / 1192	87 / 1153
Randomized Open-label	Stevens D 2002	0.069	0.026	0.112	0.002	23 / 240	6 / 220
Randomized Open-label	Kaplan S 2003	0.019	-0.005	0.042	0.119	4 / 215	0 / 101
Randomized Open-label	Kohnos S 2007	0.170	0.085	0.256	0.000	19 / 100	1 / 51
Randomized Open-label	Wunderink 2008	0.013	-0.023	0.050	0.471	1 / 75	0 / 74
Randomized Open-label		0.053	0.008	0.099	0.021	47 / 630	7 / 446
Overall		0.008	-0.003	0.020	0.161	158 / 1822	94 / 1599



*Intention-to-Treat Population. Z=1.402; P=0.161; Heterogeneity: Q=26.861; P=0.001; I2=74%

Kalil AC, et al. *BMJ Open*. 2013;3(10):e003912.

Why Should Vancomycin Be Preferred?

- **“Vancomycin is considered the gold standard for treatment of MRSA infections” – Meghan Jeffres**
- Years of experience and still very little resistance
- Preserve activity of alternative agents
- Significantly lower drug cost
- Fewer drug interactions
- Potentially lower incidence of neurotoxicity and thrombocytopenia

Jeffres MN. *Drugs.* 2017; 77(11): 1143–1154.

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Empiric Anti-MRSA Agent: Linezolid

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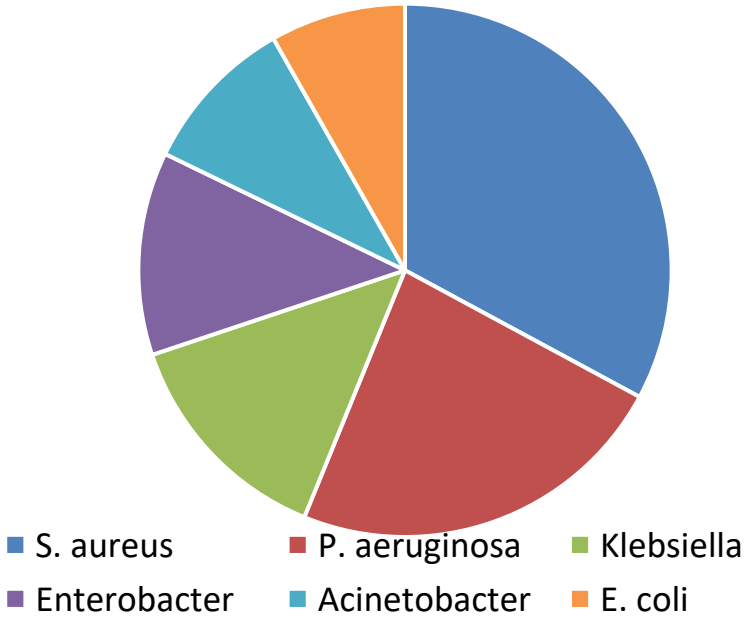
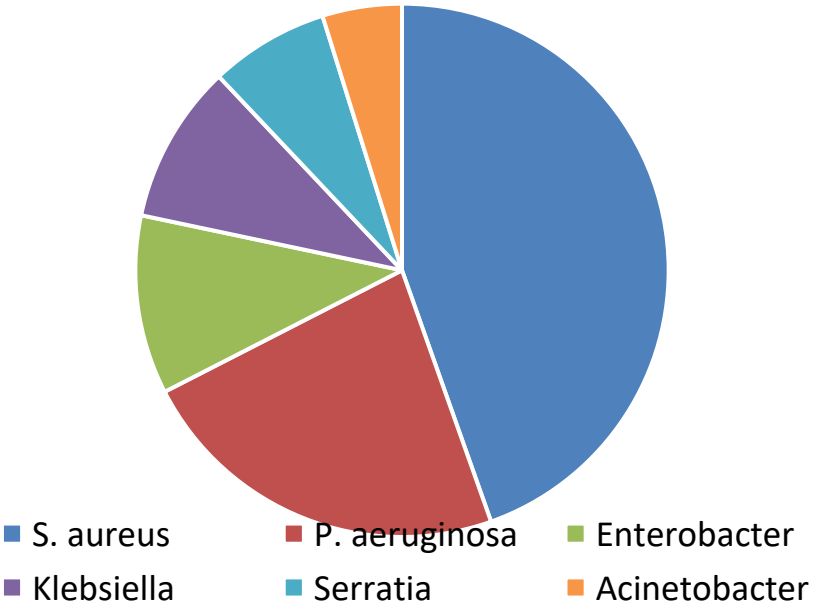
Microbiology

VAP, n=8474



HAP, n=2585



Sievert et al. Infect Control Hosp Epi. 2013;34(1):1-14.

Jones et al. Clin Infect Dis. 2010;51:S81-7.

Meta-analysis – Clinical Cure

(a) **Hospital-Acquired Pneumonia: Linezolid vs. Vancomycin: Clinical Response***

Group by Study Design	Study name	Statistics for each study: Risk difference	Lower limit	Upper limit	p-Value	Mortality / Total: Linezolid	Vancomycin
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Randomized Double-blind	Wunderink R 2012	0.021	-0.019	0.062	0.306	95 / 597	81 / 587
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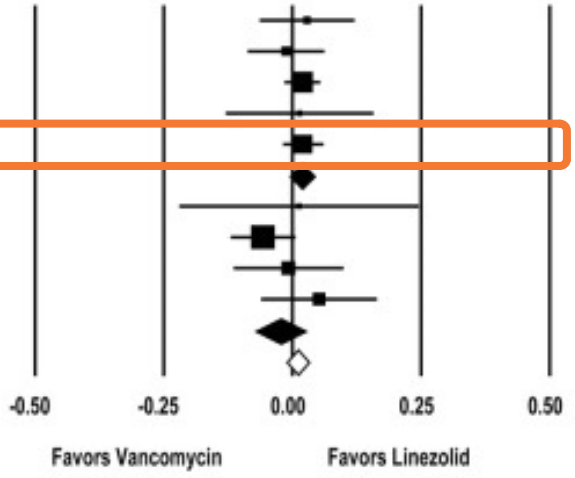


*Intention-to-Treat Population. Z=0.826; P=0.409; Heterogeneity: Q=5.878; P=0.661; I2=0%

Kalil AC, et al. *BMJ Open*. 2013;3(10):e003912.

#1 – Superior Outcomes

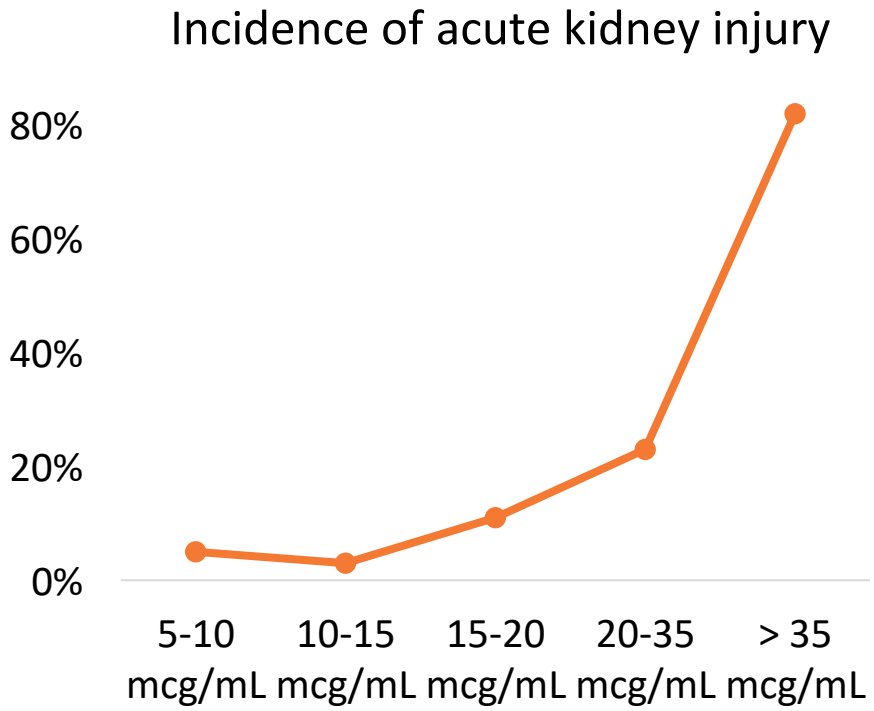
Outcomes	Linezolid	Vancomycin	ARR (95% CI)
Success EOT	150/180 (83%)	130/186 (70%)	15% (4.9-22.0)
Success EOS	95/165 (58%)	81/174 (47%)	11% (0.5-21.6)
VA cohort	**n=265**	**n=946**	**AOR (95% CI)**
30 day mortality	12%	26%	2.6 (1.7-4.0)
60 day mortality	18%	36%	2.6 (1.8-3.8)
90 day mortality	22%	42%	2.7 (1.9-3.9)

PP = per protocol
EOT = end of therapy
EOS = end of study (7-30 days after EOT)
AOR = adjusted odds ratio

Wunderink et al. CID 2012;54(5):621–9.
Reveles et al. BMC Res Notes 2015;8:450.

#2 – Less Toxicity

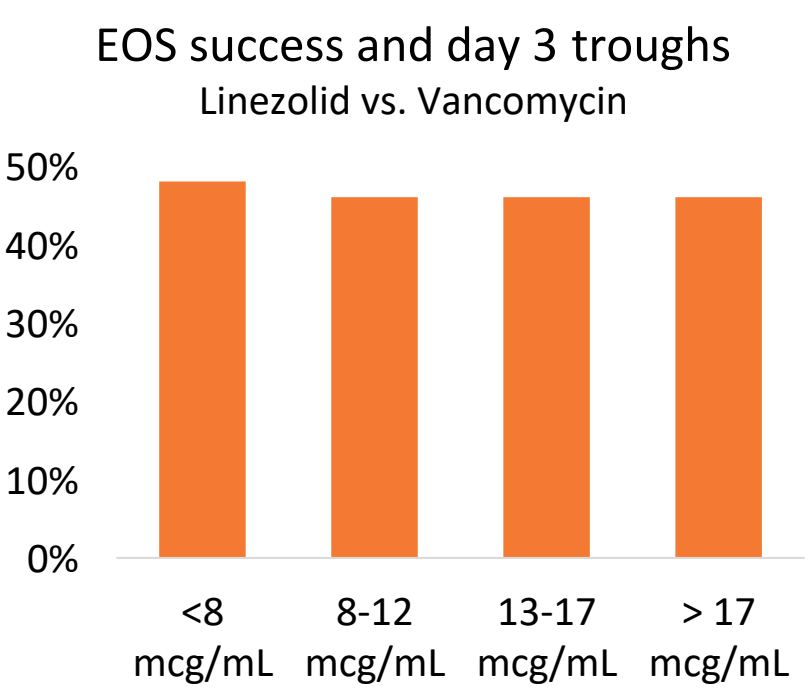
- 7 randomized controlled trials
  - 6: linezolid vs. vancomycin
  - 1: ceftaroline vs. vancomycin
- n=4033
- Acute kidney injury
  - Relative Risk = 2.42
  - Attributable risk 59%

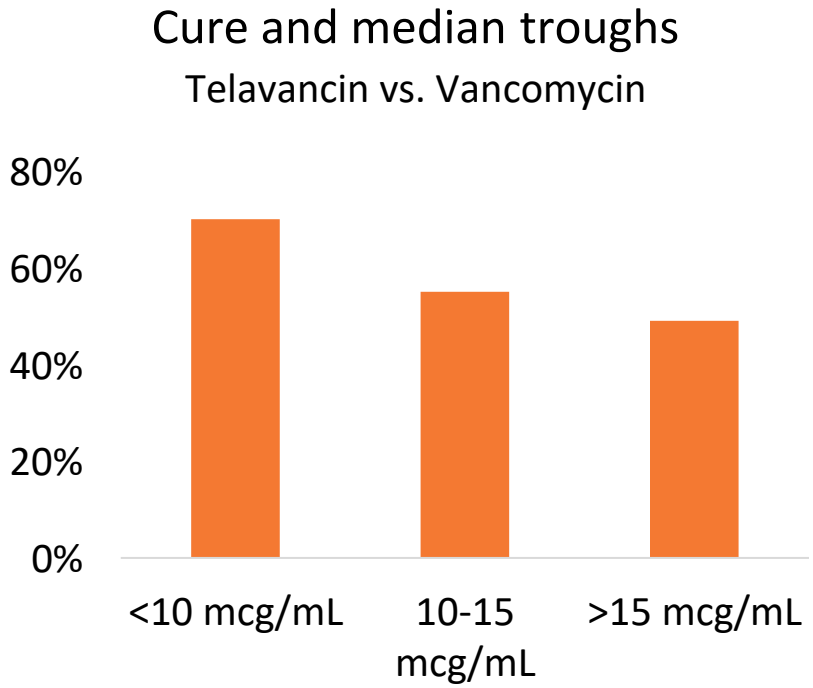


Sinha ray et al. Clin J Am Soc Nephrol. 2016;11(12):2132-2140.

Horey et al. Ann Pharmacother. 2012;46(11):1477-83.
Cano et al. Clin Ther. 2012;34(1):149-57.

#3 – No Monitoring (aka Massive Time Suck)





EOS = end of study

Wunderink et al. CID 2012;54(5):621–9.

Steinmetz et al. Clin Microbiol Infect 2015; 21: 665–673. (meta-analysis of vancomycin troughs)

Barriere et al. BMC ID 2014;14:183

#4 - Cost

Direct Costs	Vancomycin	Linezolid
Medication cost	$30 x 7 = $210	$100 x 7 = $700
Vancomycin assay	$20 x 2 = $60	$0
Total	$270	$700

Indirect costs

- Cost of treatment failure
- Cost of toxicity

Collins et al. Value in Health 2015;(18)5:614-621.

Opportunity cost, loss of potential gain from an alternative choice

Time spent monitoring vancomycin

Nursing, lab, pharmacy

Time spent on antimicrobial stewardship, transitions of care, patient education

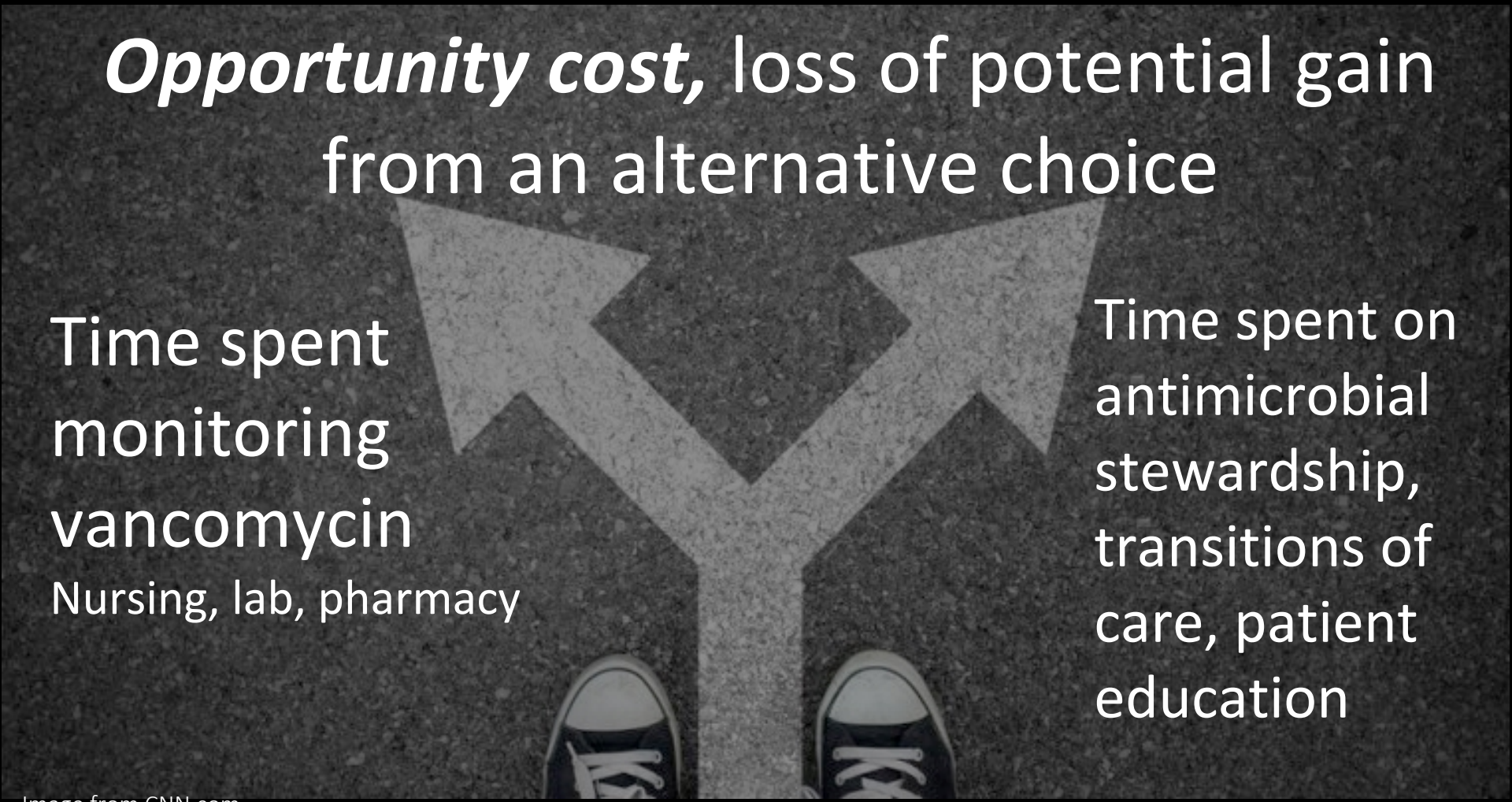


Image from CNN.com

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Empiric Anti-MRSA Agent: Vancomycin Rebuttal

Brandon Dionne, Pharm.D., AAHIVP, BCPS-AQ ID

@BWDionne

ZEPHyr Trial – Patients

- 1184 patients randomized (ITT population)
  - 484 (41%) had confirmed MRSA pneumonia (mITT population)
  - 339 (28%) included in per-protocol analysis

- Vancomycin patients had higher rates of:
  - Mechanical ventilation – 73.9% vs 66.9% (p=0.15)
  - Bacteremia – 10.8% vs 5.2% (p=0.039)
  - Chronic kidney disease – 36.9% vs 27.9% (p=0.07)

Wunderink R, et al. *Clin Infect Dis*. 2012;54(5):621-9

ZEPHyr Trial – Outcomes

- Vancomycin levels may not have been optimized
  - Median on day 3 was 12.3 mg/L (IQR 7.6-17 mg/L)
  - Median on day 6 was 14.7 mg/L (IQR 9.5-19.9 mg/L)
  - Outcomes analyzed by trough quartile?

- Pfizer had the ability to override clinical outcome decisions

- No differences in 60-day mortality
  - 15.7% for linezolid and 17.0% for vancomycin in ITT analysis
  - 28.1% for linezolid and 26.3% for vancomycin in mITT analysis

Wunderink R, et al. *Clin Infect Dis*. 2012;54(5):621-9

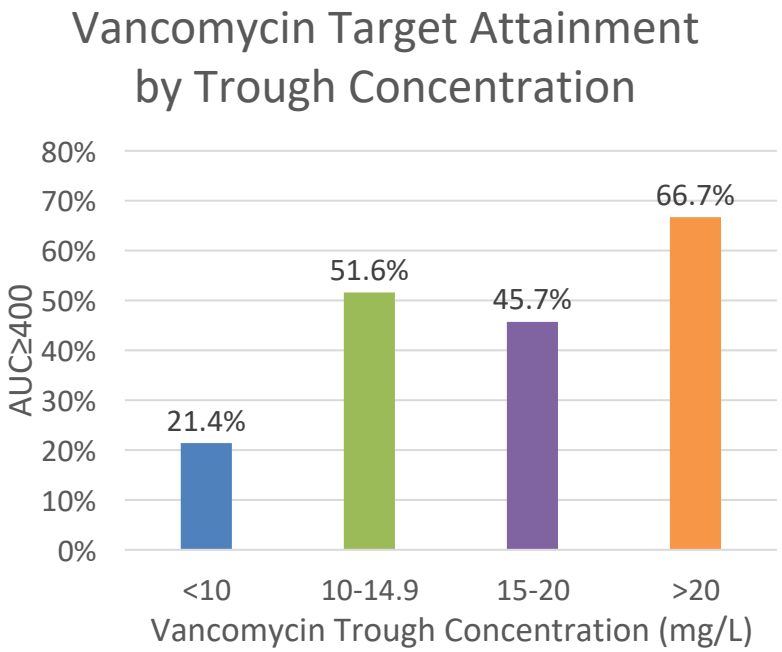
VA Cohort Study

- Population was patients age >65 years with “HCAP” from 2002-2007
- Higher proportion of vancomycin patients had VA priority score of 1 (24.8% vs 17.0%, p=0.019)
- Only 18.6% of patients were culture positive
  - More *Staphylococcus aureus* in vancomycin group (8.8% vs 1.5%, p=0.019)
  - More MRSA in vancomycin group (5.0% vs 1.9%, p=0.004)

Reveles KR, et al. *BMC Res Notes*. 2015;8:450.

Vancomycin AUC Monitoring

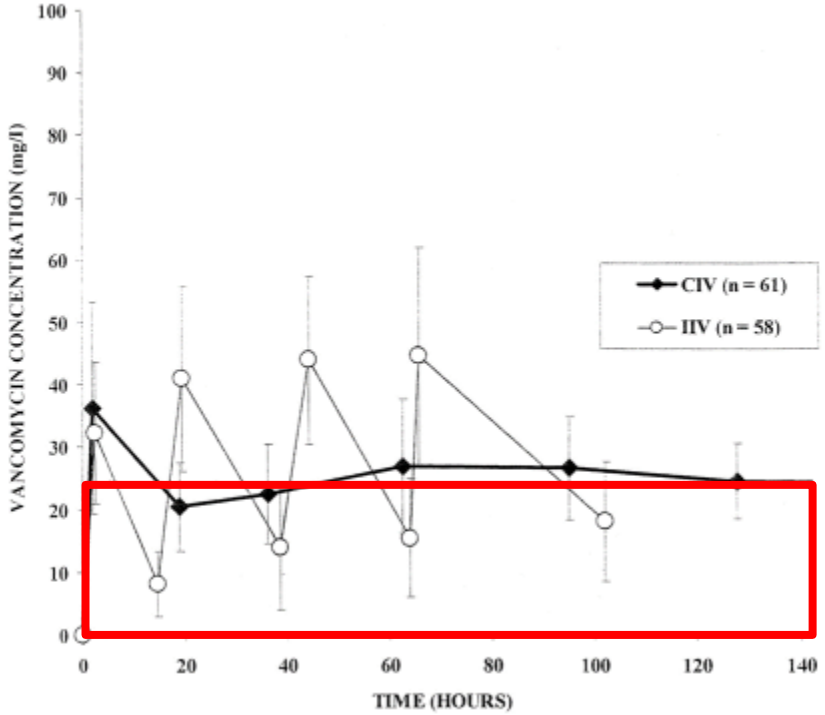
- Trough levels do not always correspond with AUC
- AUC-based dosing resulted in
  - ~50% reduction in nephrotoxicity (aOR 0.52; 95% CI, 0.34 to 0.80)
  - Fewer levels required (3.6 vs 2.4, p=0.003)
  - Similar clinical efficacy



Finch NA, et al. *Antimicrob Agents Chemother*. 2017;61(12): e01293-17.
Neely MN, et al. *Antimicrob Agents Chemother*. 2018 Jan 25;62(2): e02042-17.
Hale CM, et al. *J Pharm Pract*. 2017;30(3):329-335.

Continuous Infusion Vancomycin

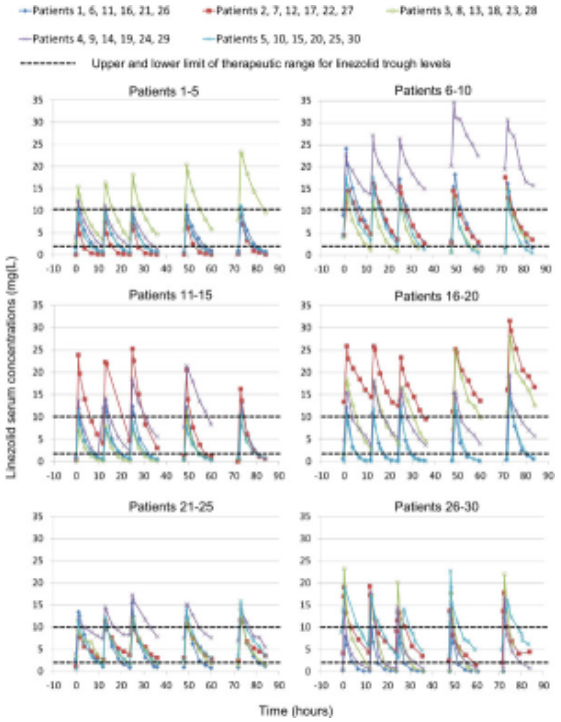
- Continuous infusion vancomycin
  - Fewer levels required for monitoring (7.7 vs 11.8, p<0.0001)
  - Less nephrotoxicity than intermittent infusion (RR 0.61; 95% CI, 0.47-0.80) with similar outcomes



Wysocki M, et al. *Antimicrob Agents Chemother*. 2001;45(9):2460-7.
Hao JJ, et al. *Int J Antimicrob Agents*. 2016;47(1):28-35.

Linezolid Monitoring?

- Significant inter- and intra-patient variability in linezolid exposure
  - Optimal AUC not achieved in 63% of patients
  - Optimal T>MIC not achieved in 50% of patients
- Strong correlation between renal clearance and linezolid clearance ($r=0.933$, $p<0.001$)
  - Renal dysfunction associated with elevated serum concentrations
  - Elevated serum concentrations associated with thrombocytopenia



Zoller M, et al. *Crit Care*. 2014;18(4):R148.
Matsumoto K, et al. *Int J Antimicrob Agents*. 2010;36(2):179-81.

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Empiric Anti-MRSA Agent: Linezolid Rebuttal

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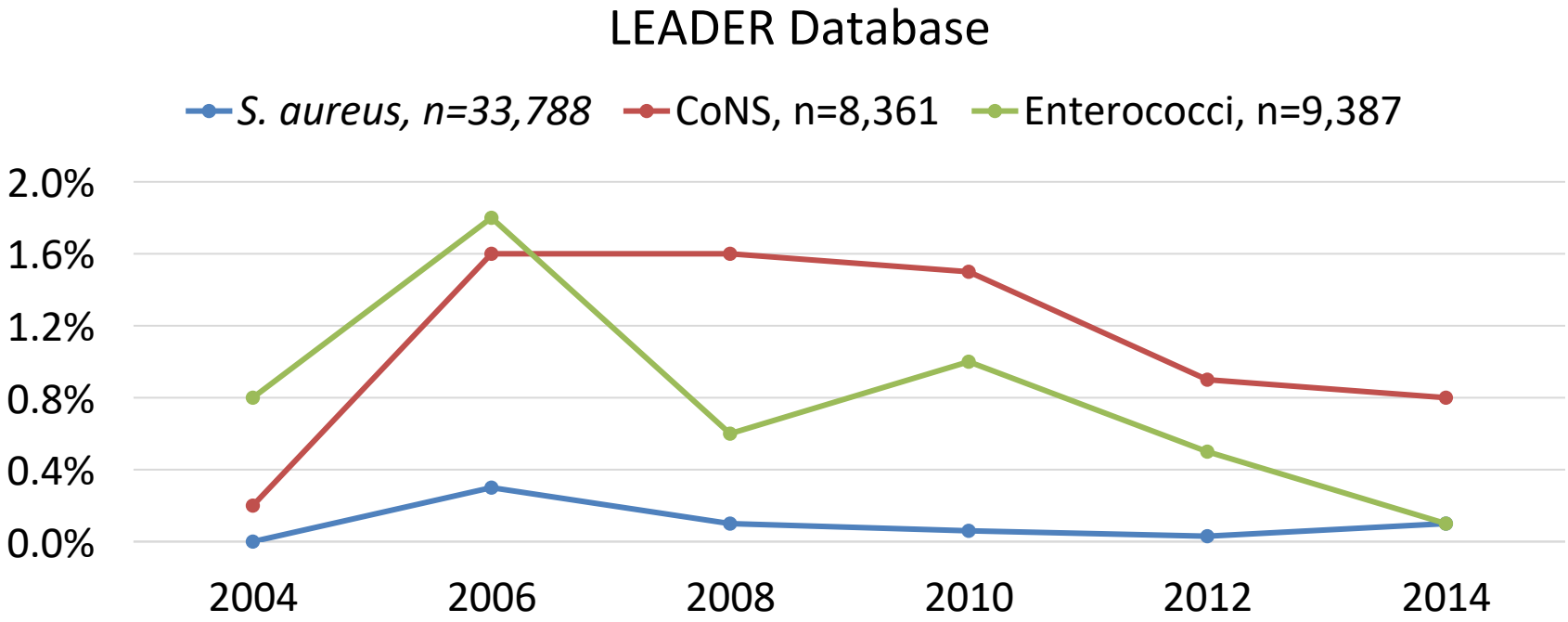
@PharmerMeg

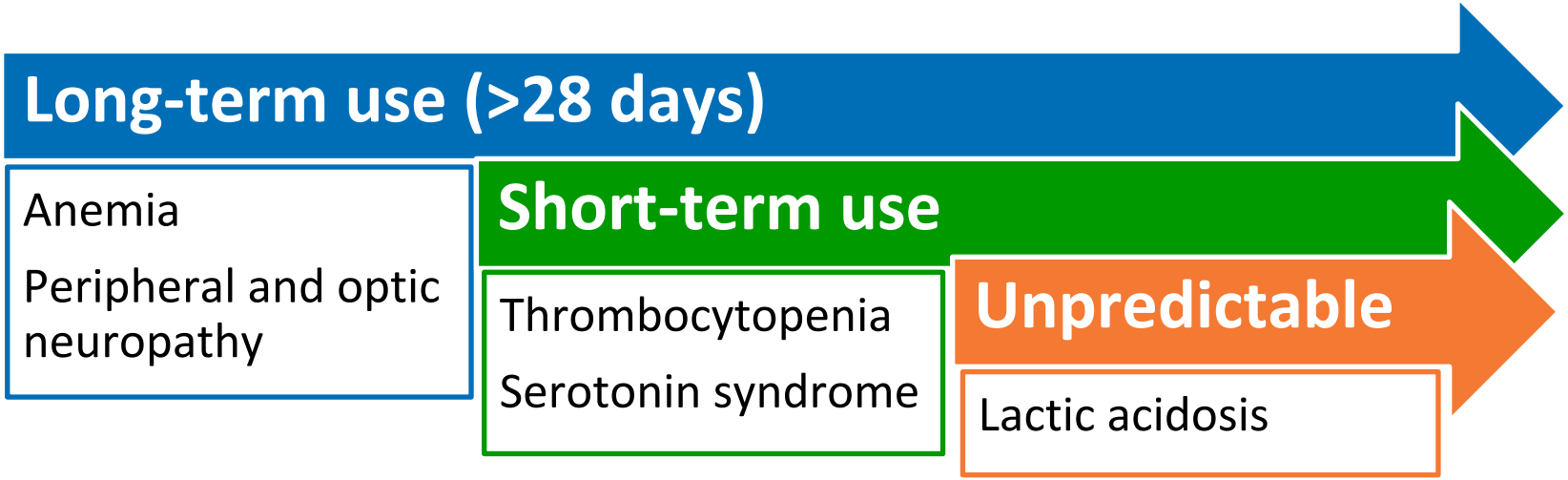
Linezolid Resistance



LEADER = linezolid experience and accurate determination of resistance

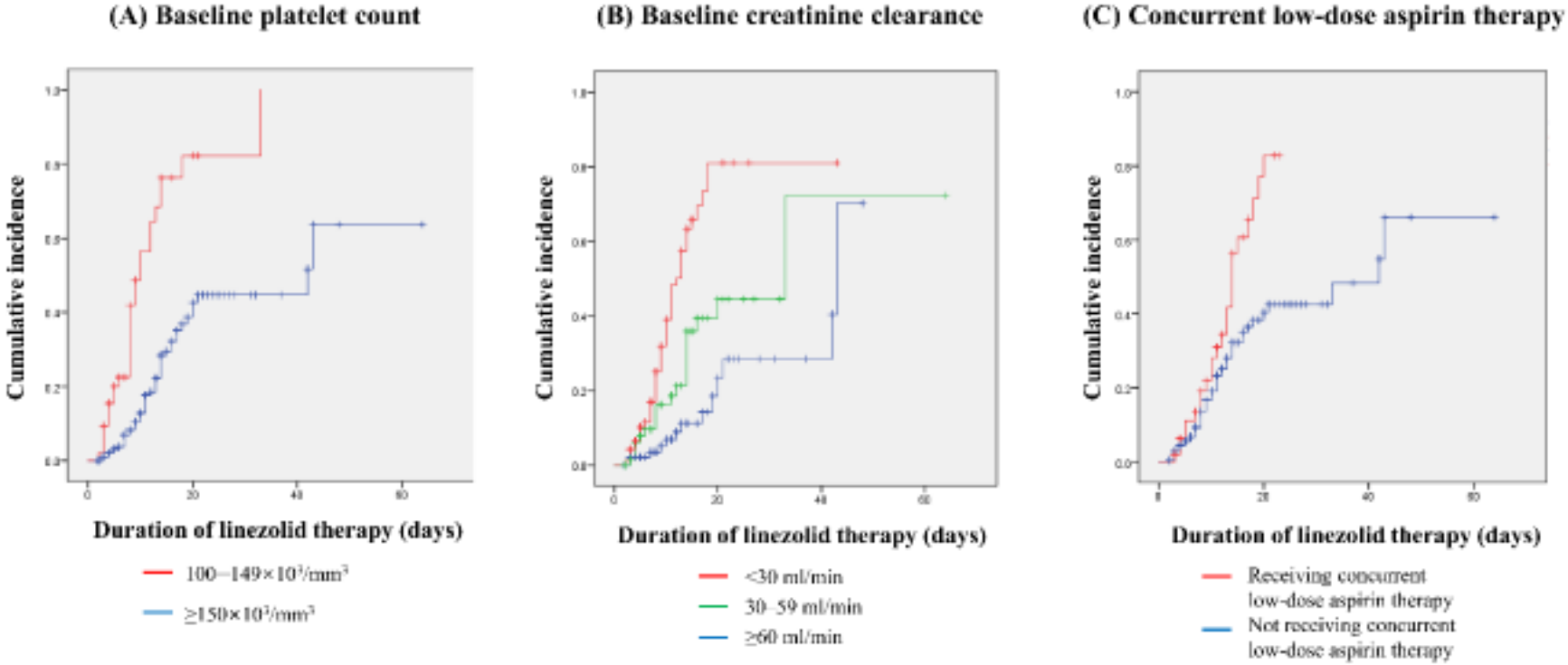
Flamm et al. Antimicrob Agents Chemother. 2016; 60(4):2273–2280.

Linezolid Adverse Events



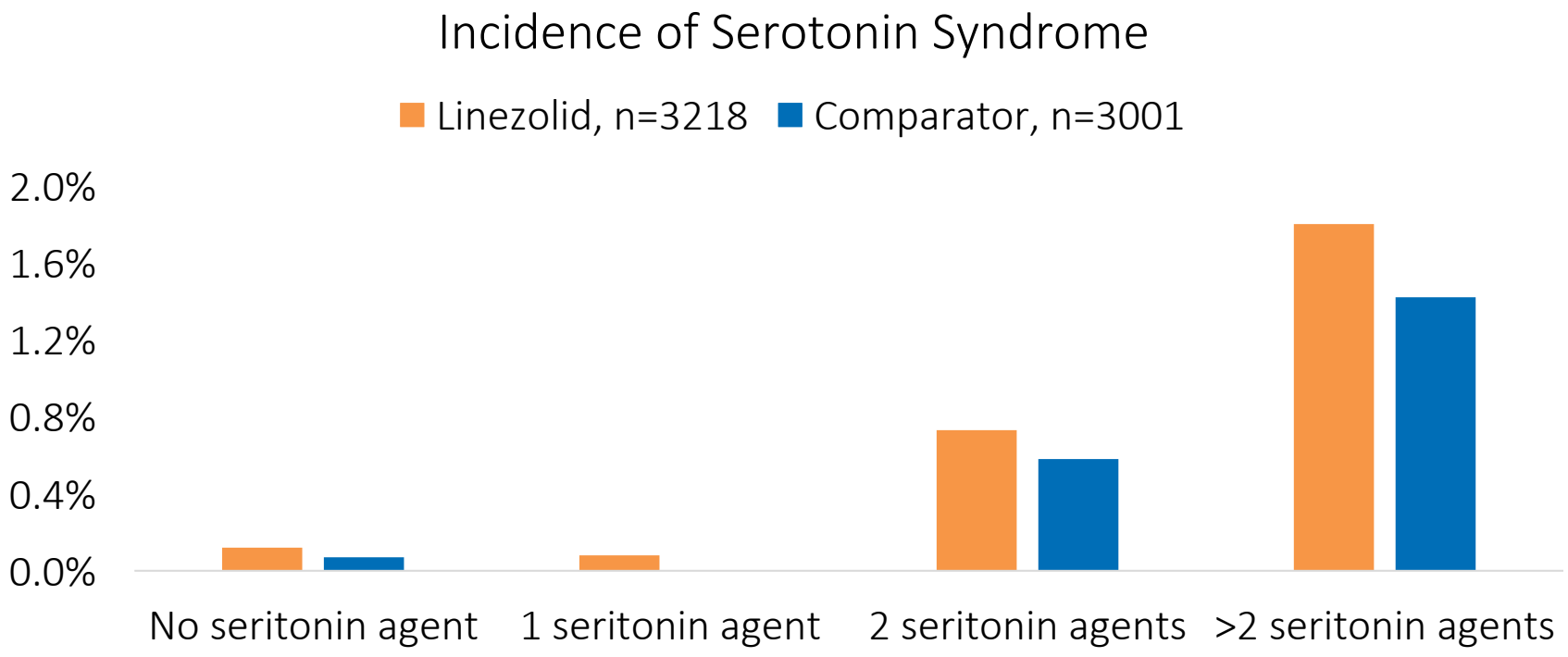
Douros et al. Expert Opin Drug Metab Toxicol. 2015;11(12):1849-1859.

Linezolid-induced Thrombocytopenia



Chio et al. Basic Clin Pharmacol Toxicol. 2018;epub.

Linezolid and Serotonin Syndrome



Butterfield et al. J Antimicrob Chemother 2012;67:494–502.

Common Ground

- Reduction in the use of anti-MRSA agents
- MRSA Nasal swabs meta-analysis = NPV 97%

	Pre-PCR, n=27	PCR, n=30	p value
Duration of vancomycin therapy	4 days ± 2	2 days ± 1	<0.01
Patients with vancomycin assays	13 (48%)	5 (17%)	0.02
Acute kidney injury	7 (26%)	1 (3%)	0.02
Mortality	4 (15%)	2 (7%)	0.41

Parente et al. CID. 2018;67(1):1–7.
Baby et al. Antimicrob Agents Chemother. 2017;61(4):e02432-16.

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Audience Poll

In a patient with nosocomial (HAP/VAP) pneumonia, which medication should be used first line as empiric therapy?

A. Vancomycin
B. Linezolid

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Vancomycin vs Linezolid for Empiric Coverage of MRSA in Nosocomial Pneumonia

Vancomycin — **Brandon Dionne** — @BWDionne

Linezolid — **Meghan N. Jeffres** — @PharmerMeg

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Vancomycin vs Fidaxomicin for *Clostridioides difficile* Infection

Fidaxomicin **Tristan Timbrook** @TimbrookTT

Vancomyin **Julie Ann Justo** @julie_justo

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Audience Poll

In a patient with *C. difficile* infection, which medication should be used first line?

A. Vancomycin
B. Fidaxomicin

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The Great ID Debates of One-Eight: Fidaxomicin treatment of *Clostridium (Clostridioides) difficile* infection

Tristan T. Timbrook, Pharm.D., M.B.A., BCPS
Antimicrobial Stewardship Pharmacist
University of Utah Health
Salt Lake City, UT

@TimbrookTT

Learning Objectives

- Recognize the guideline recommended first-line treatments for *Clostridium (Clostridioides) difficile* infection (CDI)
- Evaluate the clinical efficacy of fidaxomicin (FID) compared to vancomycin (VAN) in randomized controlled trials (RCTs) for CDI
- Appraise the clinical effectiveness of FID among real world studies
- Examine the cost-effectiveness of FID

Major Points – FID

- Decreased recurrence compared to VAN in RCTs, overall increase in global clinical cure (cure without recurrence)
- Among real world studies, FID effectiveness optimal (even in SOT, cancer, and critically ill) for decreased recurrence
- Cost-effectiveness supports first-line use

Previous 2010 Guideline Treatment Recommendations

Clinical definition	Supportive clinical data	Recommended treatment	Strength of recommendation	Quality of Evidence
Initial episode, mild or moderate	WBC < 15k and SCr < 1.5x baseline	Metronidazole	A	I
Initial episode, severe	WBC ≥ 15k and SCr ≥ 1.5x baseline	VAN	B	I
Initial episode, severe, complicated	Hypotension, shock, ileus, megacolon	VAN **AND** metronidazole*	C	III
First recurrence	---	Same as initial episode	A	II
Second recurrence	---	VAN taper or pulse	B	III

*If complete ileus, consider PR vancomycin; Cohen, SH et al. ICHE 2010.

Current 2018 Guideline Treatment Recommendations

Clinical definition	Supportive clinical data	Recommended treatment	Strength of recommendation	Quality of Evidence
Initial episode, non-severe	WBC < 15k and SCr < 1.5x baseline	VAN **OR** FID	Strong	High
Initial episode, severe	WBC ≥ 15k and SCr ≥ 1.5x baseline	VAN **OR** FID	Strong	High
Initial episode, fulminant	Hypotension, shock, ileus, megacolon	VAN **AND** metronidazole*	Strong	Moderate
First recurrence	---	VAN with taper if used initially	Weak	Low
		FID	Weak	Moderate
Second recurrence	---	Several regimens	Weak except FMT (Strong)	Low except FMT (Moderate)

FMT: Fecal Microbiota Transplantation; *If complete ileus, consider PR vancomycin; McDonald LC. *Clin Infect Dis*. 2018.

Where in therapy do the 2018 IDSA CDI guidelines place FID?

A. Strong rec, high quality evidence for initial episode, non-severe disease
B. Strong rec, high quality evidence for initial episode, severe disease
C. Equal recommendation to VAN for first recurrence but higher quality evidence for FID
D. All of the above

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FID: Efficacy

Phase 3 Studies

- Louie TJ et al, NEJM 2011
  - Population – Patients with initial CDI episode diagnosed by ≥3 diarrhea episode in 24h period and a positive CDI test
    - Excluded severe, severe complicated (toxic megacolon, etc)
  - Randomized to FID 200 mg BID or VAN 125mg QID for 10 days
  - N = 629
  - Rates of clinical cure mIIT FID 88.2% vs 85.5% VAN, 92.1% and 89.9% in PP
  - Lower rates of recurrence with FID than VAN (mITT 15.4% vs 25.3%, p=.005; PP 13.3% vs 24.0%, p=.004)
  - Notably, recurrence not different among NAP1/BI/027 strains
    - Though subgroup analysis violates randomization and therefore could relate to confounding

mIIT: modified intention-to-treat analysis; PP: per protocol

Other Phase 3 Studies

Study	Setting	Population	Treatment	Primary Outcome	Results	Notes
Cornely OA, et al. 2012. *Lancet Infect Dis.*	Multicenter EU and USA	≥ 16 yo, toxin positive CDI	FID 200mg BID vs. VAN 125 QID x 10d	Clinical cure	FID 221/252 (87.7%) vs. VAN 223/257(86.8%) (p=ns)	Among patients on concomitant antibiotics, 90.2% achieved cure with FID vs 73.3% with VAN (p=.031)
Cornely OA, et al. 2013. *J Clin Oncol.*	Posthoc analysis of two RCTs in US and Canada	Comparisons of patients with solid tumors or hematologic malignancies to those without (≥ 16y o, toxin positive CDI, ≥ 3 diarrheal events/24h)	FID 200mg BID vs. VAN 125 QID x 10d	Clinical cure	Among cancer patients, FID associated with higher global clinical cure 64/87 (73.6%) vs VAN 50/96 (52.1%) (OR = 2.56, p=0.003)	Among cancer patients, decreased recurrence with fidaxomicin (OR 0.37, p=0.018) MV analysis, VAN associated with increased recurrence

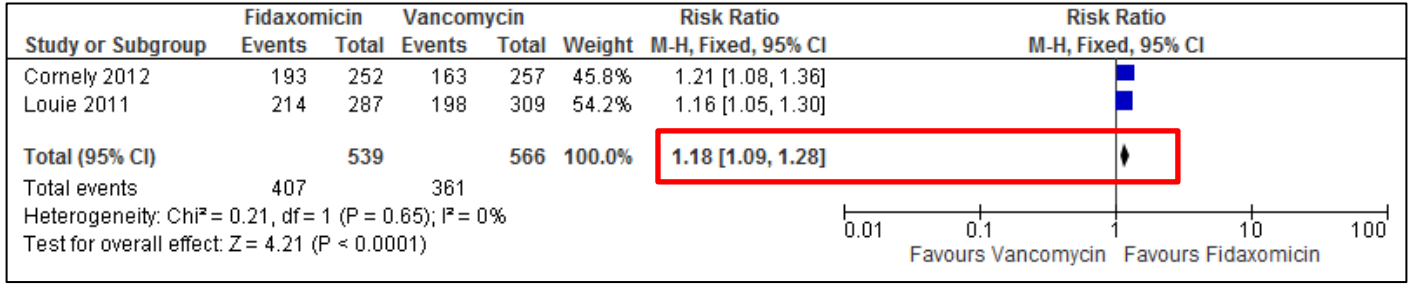
Plausibility of Decreased Recurrence with FID?

- *In vitro*, FID inhibits spore production more than VAN[1]
- *In vivo* among first episode patients, FID associated with at least $2\log_{10}$ colony-forming units/g greater reduction in spores as compared to VAN[2]
- FID associated with greater preservation of normal microbiome (*Bacteroides/Prevotella spp.*) than patients treated with VAN[3]
- Whole genome sequencing of isolates for the RCTs reflects both decrease relapse with same clonal isolate and reinfection with FID as compared with VAN ($p<0.05$)[4]
- ***Important*** as 17% of CDI patients have a 1st recurrence and 35% of those patients have a second recurrence[5]

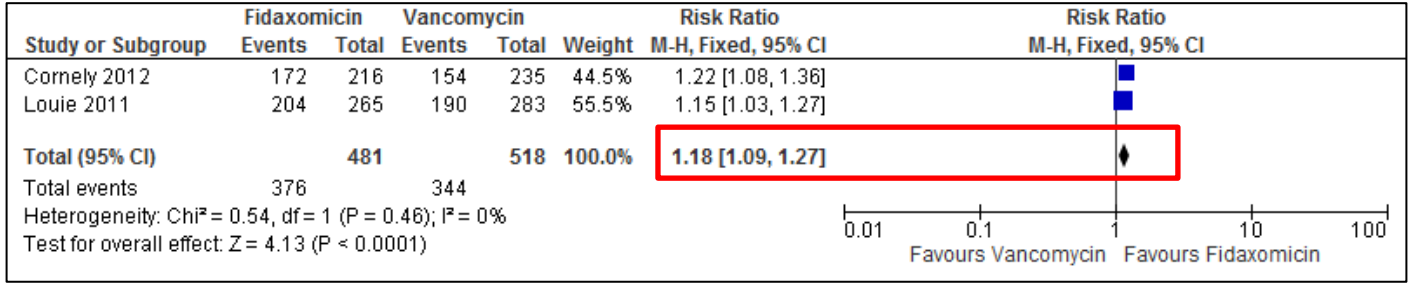
[1]*Babakhani, et al.* Clin Infect Dis 2012.; [2]Housman, et al. *ICHE. 2016;* [3]*Louie, et al. Clin Infect Dis. 2012;* [4]*Eyre et al, JID 2014.;* [5]*Reveles KR. PLoS One. 2017*

Pooled Effects of RCTs

- FID **higher** global clinical cure (cure w/o recurrence)[1] than VAN[2]
  - mITT



  - Per Protocol



[1]Nelson R. Cochrane Database Syst Rev 2007; [2]Nelson R. 2017. *Cochrane Database Syst Rev*

Pooled Effects of RCTs

Consistent with findings and interpretation from:

- Cochrane review by Nelson RL, et al. 2017. *Cochrane Database Syst Rev.;* RR 1.17 (95% CI 1.07 to 1.27)
  - *"Moderate quality evidence suggests FID is superior to VAN"*

- Beinortas T, et al. *Lancet Infect Dis*. 2017's Systematic Review and Network Meta-analysis of RCTs
  - "(for initial CDI) the highest quality evidence indicated **FID provides sustained symptomatic clinical cure most frequently**…is a **better treatment option than VAN**…"

How does the clinical efficacy of FID and VAN compare in RCTs?

A. FID associated with decreased recurrence and spore burden
B. FID associated with increased global clinical cure
C. FID associated with increased cure among patients on concomitant antibiotics for other infections
D. All of the above

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FID: Real World Effectiveness

Real-world Clinical Studies

Study	Setting / Study type	Population	Comparison	Primary Outcome	Results	Notes
Clutter AAC 2013	Multicenter EU and USA	SOT and HSCT patients	FID vs conventional therapies (VAN, metro)	Clinical cure	10/15 (67%) vs 41/44 (89%) (p=NS)	VRE colonization only occurred among patients on conventional therapies
Penziner AAC 2015	Single center retrospective	ICU or wards patients	FID among ward vs ICU	Clinical cure	67% vs 60% (p=0.9)	Similar recurrence rates 10% vs 8%
Esmaily-Fard et al, Pharmacotherapy 2014	Single center retrospective academic cancer hospital	Cancer patients with CDI treatment failure or recurrence	Descriptive results of FID use	Clinical cure	91% cure, with 82% sustained clinical cure	86% of patients were on concomitant antibiotics
Eiland et al. *Infect Dis Clin Pract.* 2015	Single center retrospective	Admitted patients with CDI	Descriptive results of FID use	Clinical success	58/60 (96.7%) clinical success	6/58 (10.3%) 90d recurrence
Spiceland et al. *J Clin Gastroenterol.* 2016.	Multicenter retrospective	CDI FID treated patients with at least 8 weeks followup	Descriptive results	Clinical response	100% among initial, 96% for 1st recurrence, 82% ≥2 recurrence	Recurrence was 0% after 1st episode, 23% after 1 prior episode, 29% after 2 or more

VRE RISK with VAN Treatment

Stevens V, et al. ECCMID 2018

- National Veterans Affairs cohort from 2006-2016 of patients with CDI and no history of VRE infection or colonization in last year
- Patients with oral VAN propensity score matched to other CDI therapies
  - Balanced on important patient characteristics, including CDI severity, comorbidities, and prior IV or oral VAN exposure
- Followed for VRE bloodstream infection or any clinical culture within 3 months
- Of 82,405 patients meeting inclusion criteria, 16,402 patients treated with oral VAN were matched 1:2 to patients who were not
- VAN treated patients were more likely to develop VRE than patients who were treated with other therapies, Relative Risk 1.48 (95% CI 1.26 – 1.75)

How does the clinical efficacy of VAN and FID compare in real world studies?

A. FID has not been shown to be associated with VRE while VAN has
B. FID has shown to be effective in SOT, HSCT, cancer patients, critically ill
C. FID has shown similar safety and efficacy to VAN
D. A and B

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FID: Cost Effectiveness

Cost Effectiveness Analyses (Simulation Studies)

Systematic reviews

- Le P, et al. *ICHE*. 2018
  - 5 databases from inception to August 2016
  - 14 studies included, decision tree model or Markov models
  - Initial CDI, FID more cost effective than VAN in 2 of 3 studies
  - For severe initial, FID most cost effective
  - For recurrent CDI, cost-effective in 3/5 studies

- Burton HE, et al. *Pharmacoeconomics.* 2017
  - OVID search through Aug 2016
  - 27 studies included
  - Fidaxomicin was cost effective vs. VAN or metro 14/24 studies (58.3%)

Real World Cost-effectiveness

- 2-year clinical and economic impact study of academic medical center use of protocol encouraging FID first line
- Compared patients on VAN or FID for CDI
  - Age ≥65, concomitant antibiotics, immunocompromised, or severe CDI
- Primary outcome: 90 day CDI readmission
- Economic evaluation based on hospital charges and insurance reimbursement for readmission, also cost of CDI therapy
- Recurrence 10/49 (20.4%) FID v.s 19/46 (41.3%) vancomycin (p=0.027)
  - Confirmed in multivariate regression (FID aOR 0.33, 95% CI 0.12 to 0.93)
- Hospital costs on average of $3,286 with FID vs $6,333 with VAN
  - Cost savings of $3,047 with FID

Gallagher JC, et al. *AAC*. 2015.

How does the cost effectiveness of VAN and FID compare?

A. Cost-effectiveness analysis (simulation studies) overwhelmingly favor VAN
B. Cost-effectiveness analysis (simulation studies) overwhelmingly favor FID
C. Real world implementation cost effectiveness studies favor FID, the majority of cost-effectiveness analysis studies favor FID
D. None of the above

KEY TAKEAWAYS

1) Overall, fidaxomicin is a more efficacious therapy than VAN as it is associated with increased global clinical cure and decreased recurrence

2) Special populations (cancer, SOT) and severe CDI also benefit from FID therapy over alternatives

3) Institutions should adopt FID as first line therapy based on clinical outcomes in addition to economic data which support its cost-effectiveness

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The Great ID Debates of One-Eight: Vancomycin treatment of *Clostridium (Clostridioides) difficile* infection

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Learning Objectives

- Recognize the recommended first-line treatments for *Clostridium (Clostridioides) difficile infection* (CDI)
- Evaluate the clinical efficacy of vancomycin compared to fidaxomicin in randomized controlled trials (RCTs) for CDI
- Evaluate the real-world implications of replacing vancomycin with fidaxomicin in the treatment of CDI

Major Points – Pro Vancomycin

- Vancomycin (VAN) now the gold standard therapy for CDI treatment
- Patient accessibility to vancomycin >>> fidaxomicin (FDX)
- Differences in CDI recurrence rates between VAN & FDX can be mitigated by other factors

IDSA/SHEA 2017 Guideline Update for CDI

Clinical Definition	Supportive Clinical Data	Recommended Treatment	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	WBC ≤ 15k and SCr < 1.5x baseline	**VAN 125 mg PO QID x10 days** OR FDX 200 mg PO BID x10 days	Strong/High
Initial episode, severe	WBC > 15k or SCr ≥ 1.5x baseline	**VAN 125 mg PO QID x10 days** OR FDX 200 mg PO BID x10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	**VAN 500 mg PO QID** **(+ Rectal VAN if ileus)** + Metronidazole 500 mg IV Q8h	Strong/Moderate, except Weak/Low for rectal VAN
First recurrence	---	**VAN PO, with taper/pulse if VAN initially** OR FDX 200mg PO BID x 10 days, if VAN initially	Weak/Low Weak/Moderate
Second or subsequent recurrence	---	Several regimens, e.g. **VAN PO taper/pulse**, FDX PO, FMT	Weak/Low, except Strong/Moderate for FMT

FDX = Fidaxomicin, FMT = Fecal microbiota transplant, RCT = Randomized controlled trial, SCr = Serum creatinine, VAN = Vancomycin, WBC = White blood cell count

1. McDonald LC, et al. Clin Infect Dis. 2018;66(7):987-994.

Where in therapy do the IDSA/SHEA 2017 updated CDI guidelines place vancomycin?

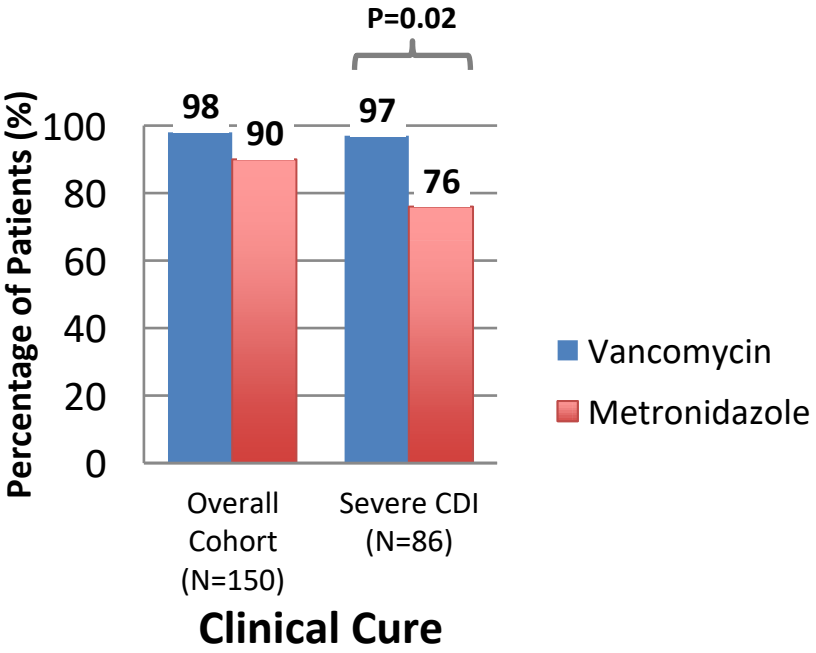
A. Strong rec, high quality evidence for initial episode, non-severe disease
B. Strong rec, high quality evidence for initial episode, severe disease
C. Recommended for fulminant CDI and/or any recurrences
D. All of the above

Proven Track Record

- No studies show superiority over vancomycin
- Vancomycin DOES show superiority over other therapies

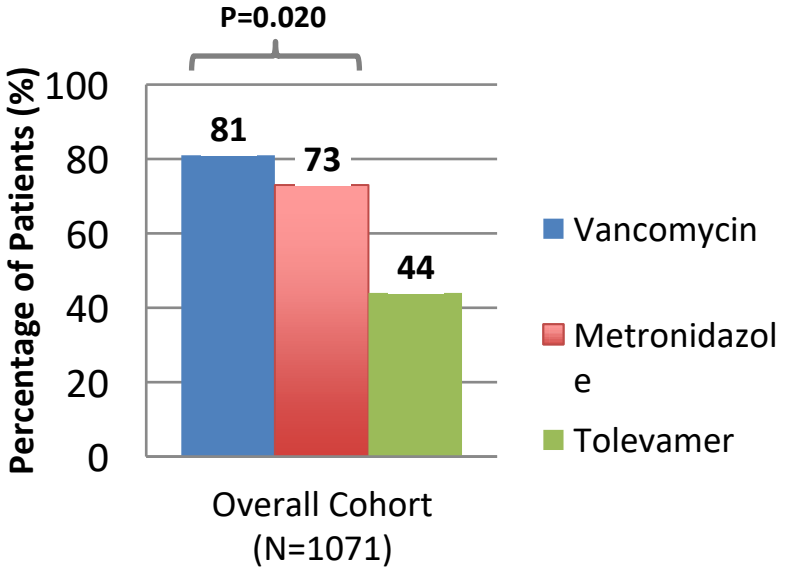
Vancomycin vs. Metronidazole

Zar et al 2007



Clinical Cure

Johnson et al 2014

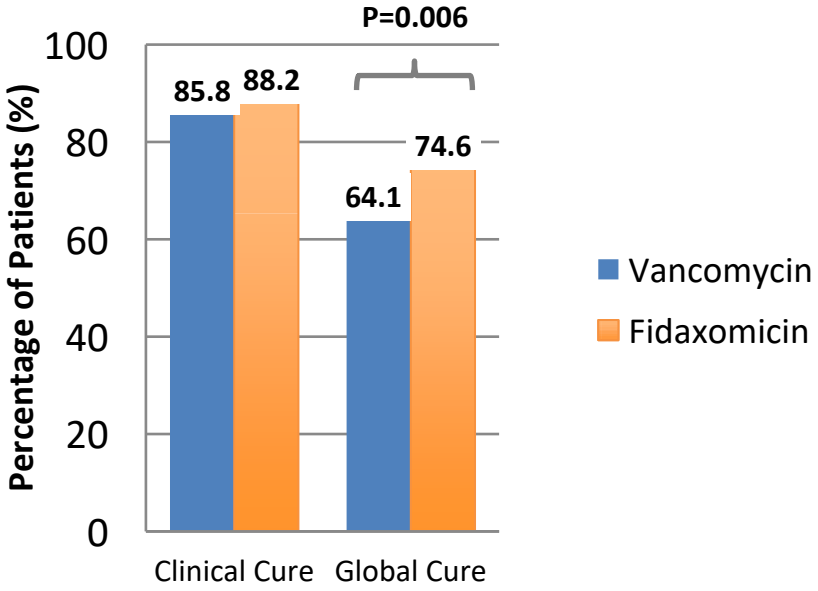


Clinical Success

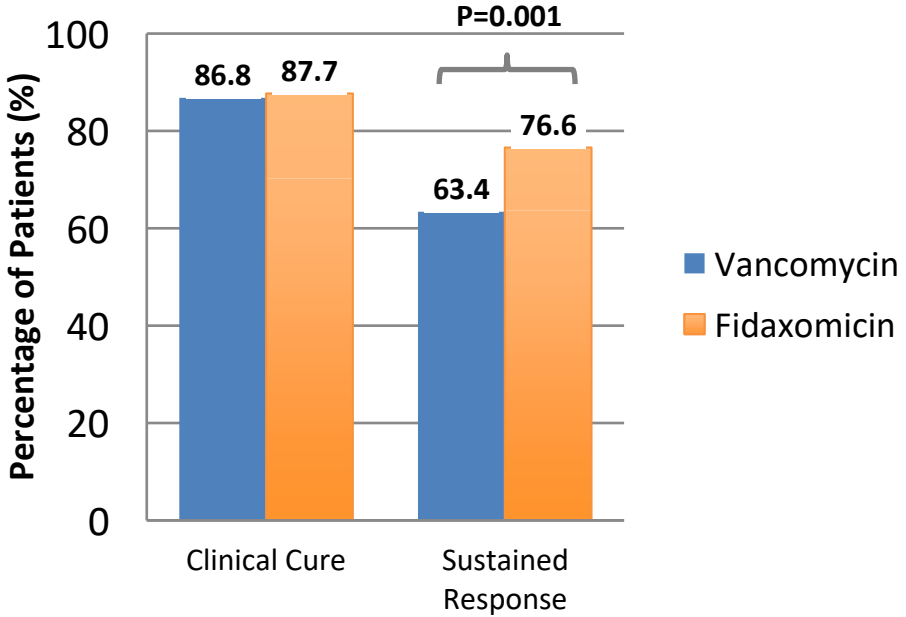
1. Zar FA, et al. Clin Infect Dis. 2007;45:302-307.
2. Johnson S, et al. Clin Infect Dis. 2014;59(3):345-354.

Vancomycin vs. Fidaxomicin

Louie et al 2011
N=596



Cornely et al 2012
N=509



1. Louie TJ, et al. N Eng J Med. 2011;364:422-431.
2. Cornely OA, et al. Lancet Infect Dis. 2012;12:281-289.

Which of the following is true regarding the clinical efficacy of vancomycin in RCTs?

A. VAN associated with decreased clinical cure vs. metronidazole
B. FDX associated with increased clinical cure vs. VAN
C. VAN associated with decreased sustained response vs. FDX
D. All of the above

Vancomycin Plays Well With Others

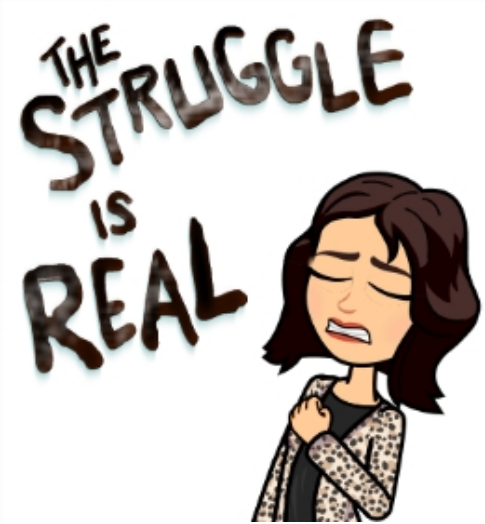
- **Accessibility:** On formulary & stocked in most pharmacies
- **Availability:** New & improved RECONSTITUTED oral vancomycin solution
  - Removes need for “compounding”
- **Administratibility:** Capsule and liquid formulations
  - Any oral entry = drug delivery
- **Affordability:** Covered by most/all major payors
  - Generic product!

Price Comparison

Drug	Regimen	Average Wholesale Price[1]	Estimated Cost for 10-day Supply
Vancomycin	125 mg PO QID x 10 days	Firvanq® 50mg/mL reconstituted solution: $1.00 per mL (150 mL, 300 mL)	$1 x 150 mL = **$150**
		Vancomycin HCl 125 mg: $31.33 per capsule	$31 x 40 caps = **$1,240**
		Vancocin® 125 mg: $94.38 per capsule	$94 x 40 caps = **$3,760**
		Vancomycin compounded oral solution	**~$60 (varies)[2]**
Fidaxomicin	200 mg PO BID x 10 days	Dificid® 200 mg: $220.90 per tablet	$220 x 20 tabs = **$4,400**
Metronidazole	500 mg PO TID x 10 days 500 mg IV Q8h	Metronidazole 500 mg PO: $0.26-$0.93 per tablet	$0.60 x 30 caps = **$18**
		Metronidazole 5 mg/mL IV: $0.01-$0.06 per mL	$0.03 x 3,000 mL = **$90**

1. Lexi-Drugs. Lexicomp. Wolters Kluwer Clinical Drug Information, Inc. Hudson, OH. Accessed on October 1, 2018 at: http://online.lexi.com
2. Personal communication with Palmetto Health Richland Hospital Pharmacy on October 1, 2018.

Deployability of First-Line Fidaxomicin?



- Difficult to determine those at highest risk for CDI recurrence
  - → Give fidaxomicin to everyone?
- Real-life hurdles of payment for fidaxomicin ($$$)
- Time needed to secure access, e.g. prior authorization, also costly to healthcare system

Preventing CDI Recurrence

- Benefit of fidaxomicin is compared to vancomycin x 10 days
- Why not extend, taper, and/or pulse vancomycin?
  - Vancomycin taper/pulse is an accepted option for first recurrence [1,2]
    - Option for those at high risk of first recurrence too?
  - More vancomycin is still cheaper than a course of fidaxomicin
- Why not give vancomycin in combination with more economical (& likely more effective) non-antibiotic therapies?

1. McDonald LC, et al. Clin Infect Dis. 2018;66(7):987-994.
2. Debast SB, et al. Clin Microbiol Infect. 2014;20 Suppl 2:1-26.

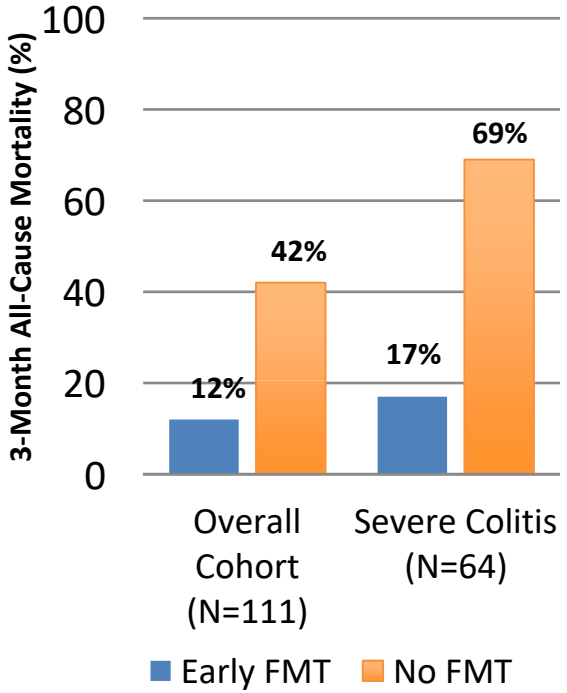
Early Fecal Microbiota Transplant (FMT)?

- Observational cohort of CDI (N=111) in France
- Evaluated all-cause 3-month mortality with early FMT vs. no FMT
  - Adjusted OR 0.13 (95% CI 0.04-0.44, p=0.001)

Number needed to treat to save 1 life at 3 months in *severe* CDI cases:

2

- Limitations:
  - Elderly cohort (median age 81-83 years)
  - Unblinded investigators



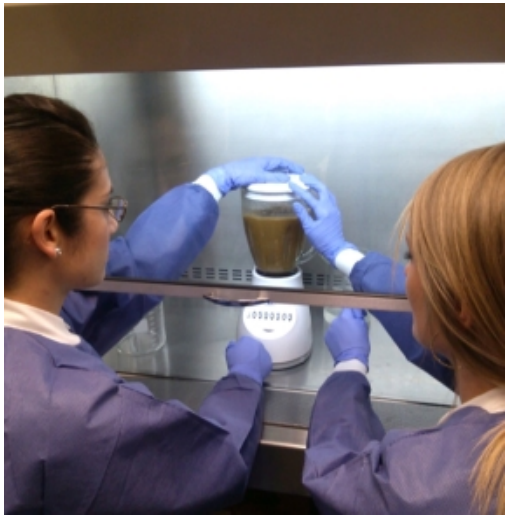
1. Hocquart M, et al. Clin Infect Dis. 2018;66(5):645-650.

Early Kefir?

- Case series of recurrent CDI (N=25)[1]
- 8-week course of staggered and tapered antibiotic withdrawal (STAW) regimen with metronidazole (N=4) or VAN (N=21)
  + **Probiotic liquid kefir** 150 mL PO TID with meals
- 84% (21/25) remained free of diarrheal symptoms at 9 months
  - 16% (4/25) patients relapsed, but were successfully treated with VAN x 14 days, followed by rifaximin x 14 days
- Counseling point for all CDI?

1. Bakken JS. Clin Infect Dis. 2014;59(6):858-861.
2. Gustafson A. Flickr. Accessed on October 1, 2018 at https://www.flickr.com/photos/aarongustafson/197059871.

Multiple CDI Recurrences



- Let’s be real…just give me the poop, please.

Fear Mongering

- Concern for emergence of vancomycin-resistant enterococci (VRE)?

Brief pause for Dr. Timbrook to indicate where the IDSA/SHEA CDI guidelines state that oral vancomycin is a risk factor for VRE acquisition

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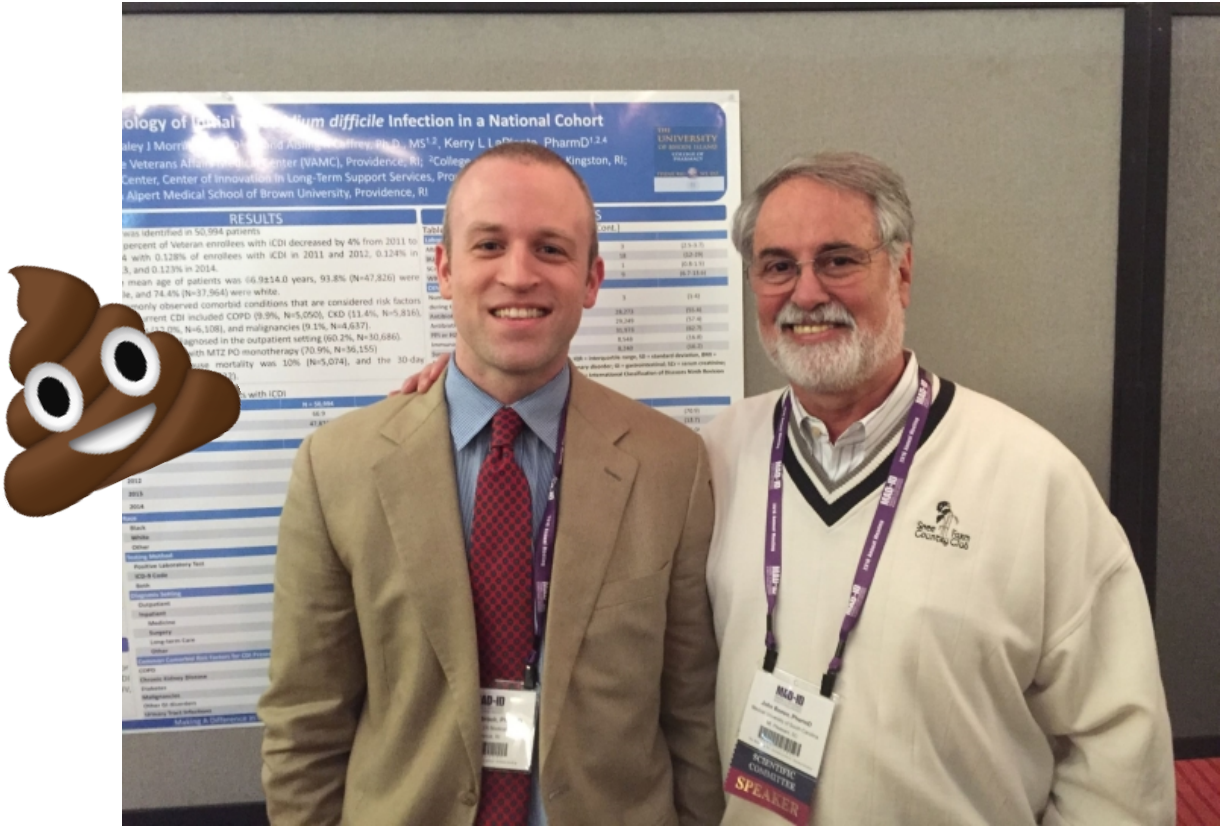
Fidaxomicin for Everyone?

Does It Pass the Mentor “Sniff” Test?



KEY TAKEAWAYS

- Vancomycin now the gold standard therapy for CDI treatment
  - Including non-severe, severe, fulminant disease and/or recurrence
- Patient accessibility to vancomycin >>> fidaxomicin
  - Oral vancomycin now available as reconstituted oral solution or generic capsules (or compounded product if still available locally)
  - Fidaxomicin remains exceedingly expensive for many patients/payers
- We should explore more economical options to ↓ the CDI recurrence rate
  - Vancomycin taper/pulse, adjunctive FMT or kefir, etc.

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ReBUTTal: FID For Your Father, VAN For Your Father-in-law

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Antimicrobial Stewardship Pharmacist
University of Utah Health
Salt Lake City, UT

@TimbrookTT

Why Not FID for Everyone?

- Obviously FID is a better drug for global clinical cure and decreased recurrence
- Economic analysis reflects better overall impact
- Possible proposed problem:
  - May not be able to justify FID first line for everyone
- The **REAL** problems:
  - Over diagnosis of CDI with molecular testing
  - Risk of recurrence not reliably predictable

Overdiagnosis of CDI: Fix Your Testing

Issue:

- Most labs performing PCR for CDI detection
  - Does **not** detect toxin production and therefore **may reflect colonization**
  - CDI rates often reported to double after switching to PCR

Solutions:

- Increase pre-test probability of disease with EHR modifications
  - Discourage testing if
    - Recent laxatives, tube feeds
    - Insufficient stooling criteria
  - ESCMID recommends and IDSA acknowledges multistep testing algorithms with different technologies can help to mitigate inappropriate diagnosis

McDonald LC, et al. *Clin Infect Dis.* 2018.

Risk Scores: Better Than Guessing but Perfect?

- Possible solution?: CDI initial episode recurrence risk score[1]
  - Low risk (8.9%; 0-2 pts)
  - Medium risk (20.2%; 3-5 pts)
  - High-risk (35%; 6-8 pts)

- Caution overestimation of prediction reliability from risk scores
  - MRSA nasal colonization outperforms risk scores for predicting MRSA BSIs and wound infections[2,3]
  - Genotypic detection out performs multiple risk scores for ceftriaxone non-susceptibility in *Enterobacteriaceae* bloodstream infections[4]
    - AUC 92.3% vs 68.7-71.1% (86-89% original studies)
  - In general, risk models suffer in performance in other populations due to "overfitting" in source cohort[5]

CDI 1st Recurrence Risk Score

Risk Factor	Points
Prior 3rd or 4th generation Cephalosporins	1
PPI	1
Prior anti-diarrheals	1
Non-severe CDI	2
Community-onset CDI	3

*During 90 days prior

[1]Reveles KR, et al. *Pharmacotherapy*. 2018; [2]Acquisto NM, et al. Emerg Med J 2018; [3]Butler-Laporte, et al BMC Infect Dis 2018; [4]Cwengros et al, IDWeek 2018; [5]Pavlou, et al. *BMJ*. 2015

Risk Factors: Can You Tell Who Is At High Risk Of Recurrence?

- Seven hospitals in UK started using FID
- Methods
  - Include patients with positive CDI test, ≥ 3 diarrheal episodes/24h, excluded patients with CDI in last 3 months
  - Hospitals had different use protocols
  - At the two hospitals (A&B) using FID first line for everyone while others (C-G) used only in select patients
- Results
  - At hospitals A&B recurrence for initial fell from 10.6-16.3% to 3.1%, mortality dropped significantly as well ($p<0.05$)
  - Hospital C-G had overall minimal changes and in one hospital recurrence increased

Goldenberg et al. *Microbiol Infect Dis.* 2016.

In Closing: CDI Treatment For Your Favorite Colleague

Julie,

Would you give your friend and beloved coworker, Brandon Bookstaver vancomycin for CDI?

*Adapted from MADID 2017 Sheetz vs Lodise debate

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ReBUTTal: Pro Vancomycin

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Cost-Effectiveness Data

- For 1st recurrence of CDI, compared FDX, VAN, or VAN + bezlotoxumab
- Outcome: Incremental cost-effectiveness ratio (ICER)
  - Payer's perspective
  - Willingness-to-pay (WTP) threshold of $100,000

VAN
Cost/pt: $15,692
QALYs/pt: 0.8019

FDX
Cost/pt: $17,047
QALYs/pt: 0.8046

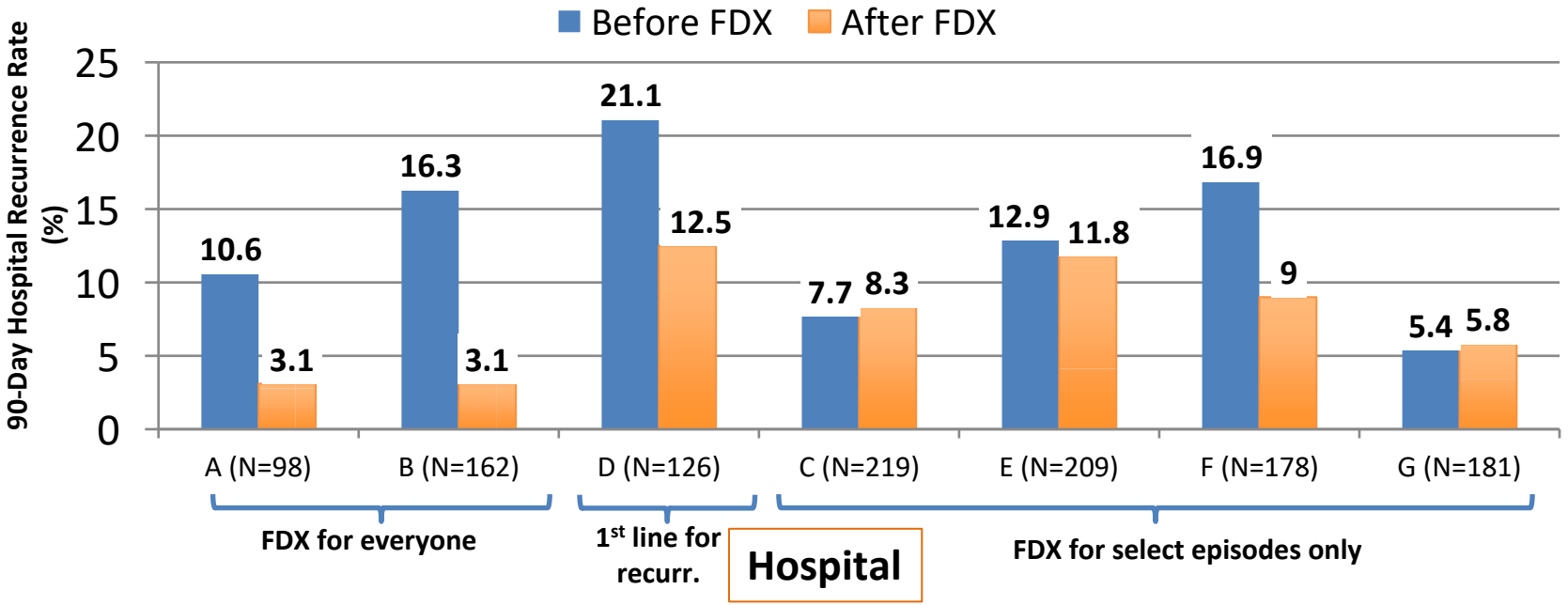
ICER for FDX vs. VAN
(Cost per additional QALY gained)
$500,975

  - VAN has 68.4% probability of being the most cost-effective
    - Only 29.2% for FDX and 2.4% for VAN + bezlotoxumab

1. Lam SW, et al. Infect Dis Hosp Epidemioogy. 2018;39(8):924-930.

Expanding Fidaxomicin Use in the Real-World

- 7 hospitals in the United Kingdom included FDX in their clinical protocols between 2012-2014



1. Goldenberg SD, et al. Eur J Clin Microbiol Infect Dis. 2016;35:251-259.

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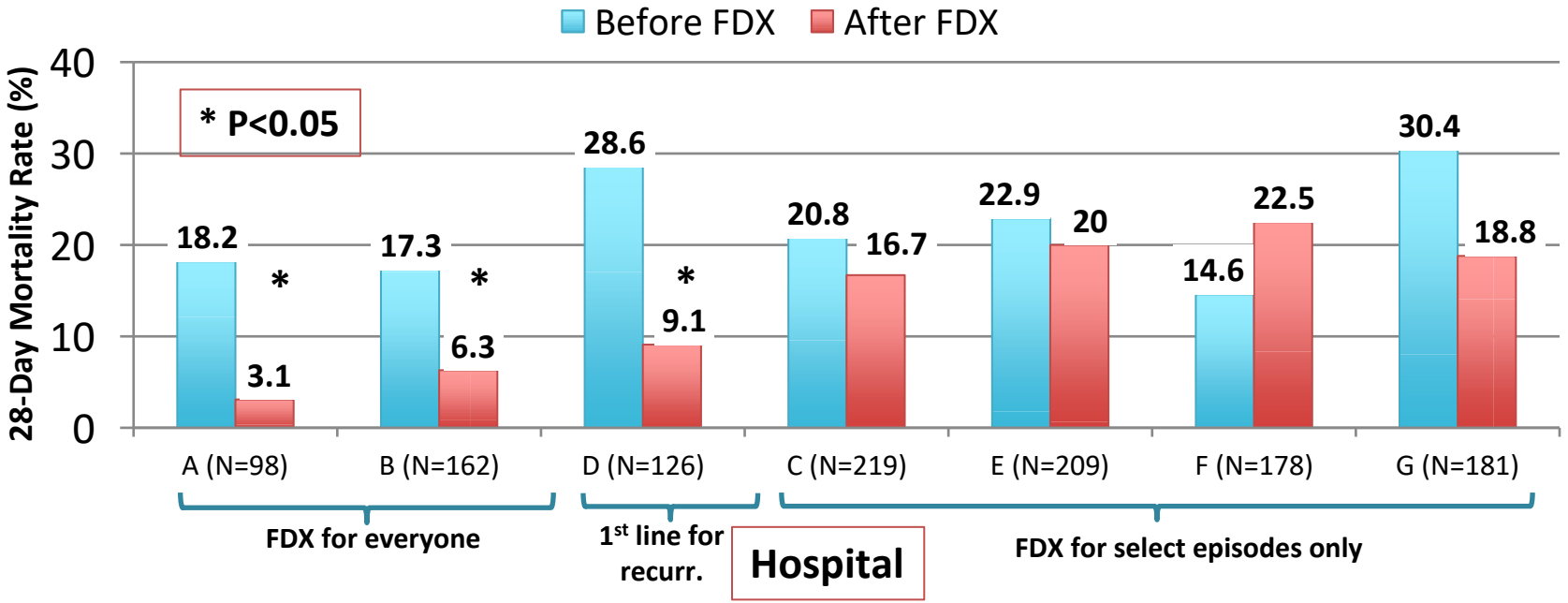

1. Goldenberg SD, et al. Eur J Clin Microbiol Infect Dis. 2016;35:251-259.

Expanding Fidaxomicin Use in the Real-World

Outcome	Finding
CDI recurrence rates	Absolute ↓ of ~10% with FDX for all (Hospital A, B)
Length of stay	↑ or stayed the same
Time to resolution of diarrhea	↑ or stayed the same

- Discrepancies:
  - Hospitals E & F actually had 49%-66% FDX use in post period
    - Yet had comparable outcomes in recurrence and mortality??
  - Hospital D had only 7% (4/56) FDX use in post period
    - Yet still managed to significantly ↓ recurrence rate and mortality??
- **Lesson:** Difficult to predict the impact of expanding your local FDX use

1. Goldenberg SD, et al. Eur J Clin Microbiol Infect Dis. 2016;35:251-259.

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Audience Poll

In a patient with *C. difficile* infection, which medication should be used first line?

A. Vancomycin
B. Fidaxomicin

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Vancomycin treatment of *Clostridium (Clostridioides) difficile* infection

Fidaxomicin	**Tristan Timbrook**	@TimbrookTT
Vancomyin	**Julie Ann Justo**	@julie_justo

KEY TAKEAWAYS

1) **VANCOMYCIN IS THE GOLD STANDARD – PRO VANCOMYCIN**
We have used vancomycin for 50 years with vancomycin with very little resistance. Increasing linezolid use had been shown to cause spikes in resistance.

2) **OPPORTUNITY COST OF VANCOMYCIN – PRO LINEZOLID**
Time spent monitoring vancomycin can and should be reallocated to activities proven to improve patient care, outcomes, and institutional costs.

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3) **FIDAXOMICIN IS MULTIFACETED – PRO FIDAXOMICIN**
Higher upfront cost results in increased global cure, decreased recurrence, & proven cost-effectiveness.

4) **VANCOMYCIN IS THE GOLD STANDARD – PRO VANCOMYCIN**
Recommended for ALL types of CDI. Fidaxomicin isn't the answer – call for research for more economical solutions.

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The Great ID Debates of One-Eight

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