Current Clinical Controversies & Debates in Infectious Diseases

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Disclosures

- The presenters have no real or perceived conflicts of interest related to this presentation

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Learning Objectives

At the end of this session, participants should be able to:

1. Recognize novel and non-traditional metrics to measure the success of antimicrobial stewardship programs
2. Identify infections conventionally treated with intravenous therapy that may be candidates for oral beta-lactam therapy
3. Recall the role of fidaxomicin and vancomycin in treatment of *C. difficile* based on updated treatment guidelines, literature and practical considerations

CLINICAL CONTROVERSY #1
Antimicrobial Stewardship Metrics

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Traditional Antimicrobial Stewardship Metrics

- Antibiotic Use Measures
  - Days of therapy (DOT)
  - NHSN AU Option → Standardized Antimicrobial Administration Ratio (SAAR)
  - Defined daily doses (DDD)
- Outcome Measures
  - *C. difficile* infections
  - Antibiotic resistance
  - Financial impact
- Process Measures for Quality Improvement
  - Types and acceptance of recommendations from prospective audit and feedback
  - Preauthorization interventions
  - Adherence to facility-specific treatment guidelines and if feasible, by prescriber
  - Others: antibiotic timeouts, medication use evaluations (MUE), IV to PO, duplicate therapy, appropriate discharge antibiotic selection and duration

CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. Available at https://www.cdc.gov/antibiotic-use/core-elements/hospital.html.

Antibiotic Use Measures

Days of Therapy (DOT)

- Sum of days for which any amount of antimicrobial was given to individual patients
- Should be adjusted for patient-days or admissions
- Standard utilization metric that can show dedicated pharmacist role in antimicrobial stewardship decreases antibiotic use; when that role is removed, antibiotic use increases

	Effect of ASP addition, change in trend of DOT/ 1000 patient-days per month	P	Effect of ASP discontinuation, change in trend of DOT/ 1000 patient-days per month	P
Total antibiotics	-24.38	< 0.001	30.16	< 0.001
Restricted antibiotics	-4.03	< 0.001	7.06	< 0.001
Broad-spectrum antibiotics	-7.02	0.011	6.56	0.019
Carbapenems	-2.85	< 0.001	3.94	< 0.001
Glycopeptide	-0.81	0.169	2.98	< 0.001

Jang W, Hwang H, Jo HU, Cha YH, Kim B. Effect of discontinuation of an antimicrobial stewardship programme on the antibiotic usage pattern. *Clin Microbiol Infect*. 2021 Dec;27(12):1860.e1-1860.e5. doi: 10.1016/j.cmi.2021.07.019. Epub 2021 Jul 27.

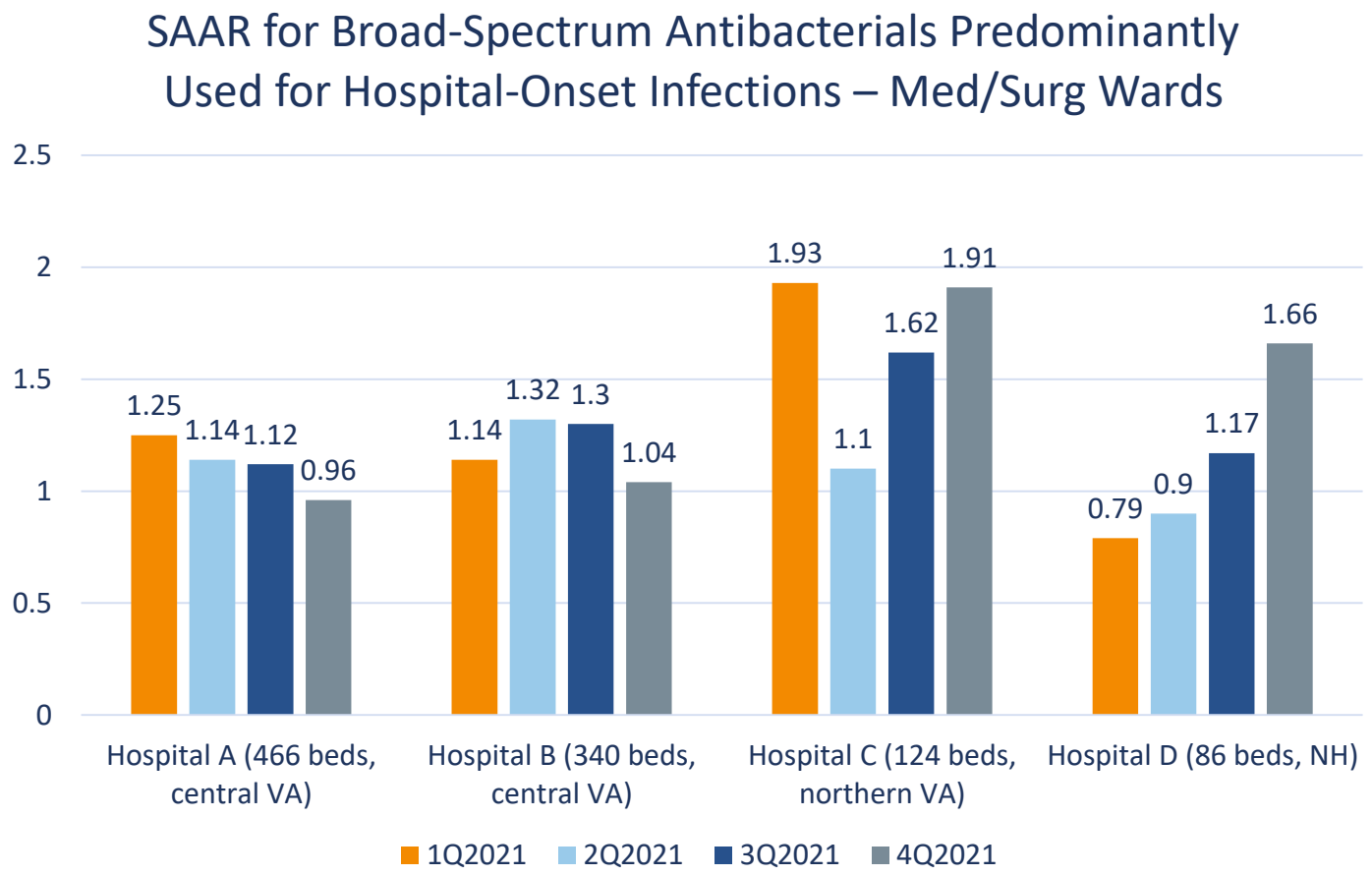
Antibiotic Use Measures

NHSN AU Option → SAAR (Standardized Antimicrobial Administration Ratio)

- SAAR – what an institution's antibiotic use is compared to what it should be
- Based on DOT, but is risk adjusted for hospital-level and unit-level factors
- Calculation:

$$\text{SAAR} = \frac{\text{Observed antimicrobial use (DOT)}}{\text{Predicted antimicrobial use (DOT)}}$$

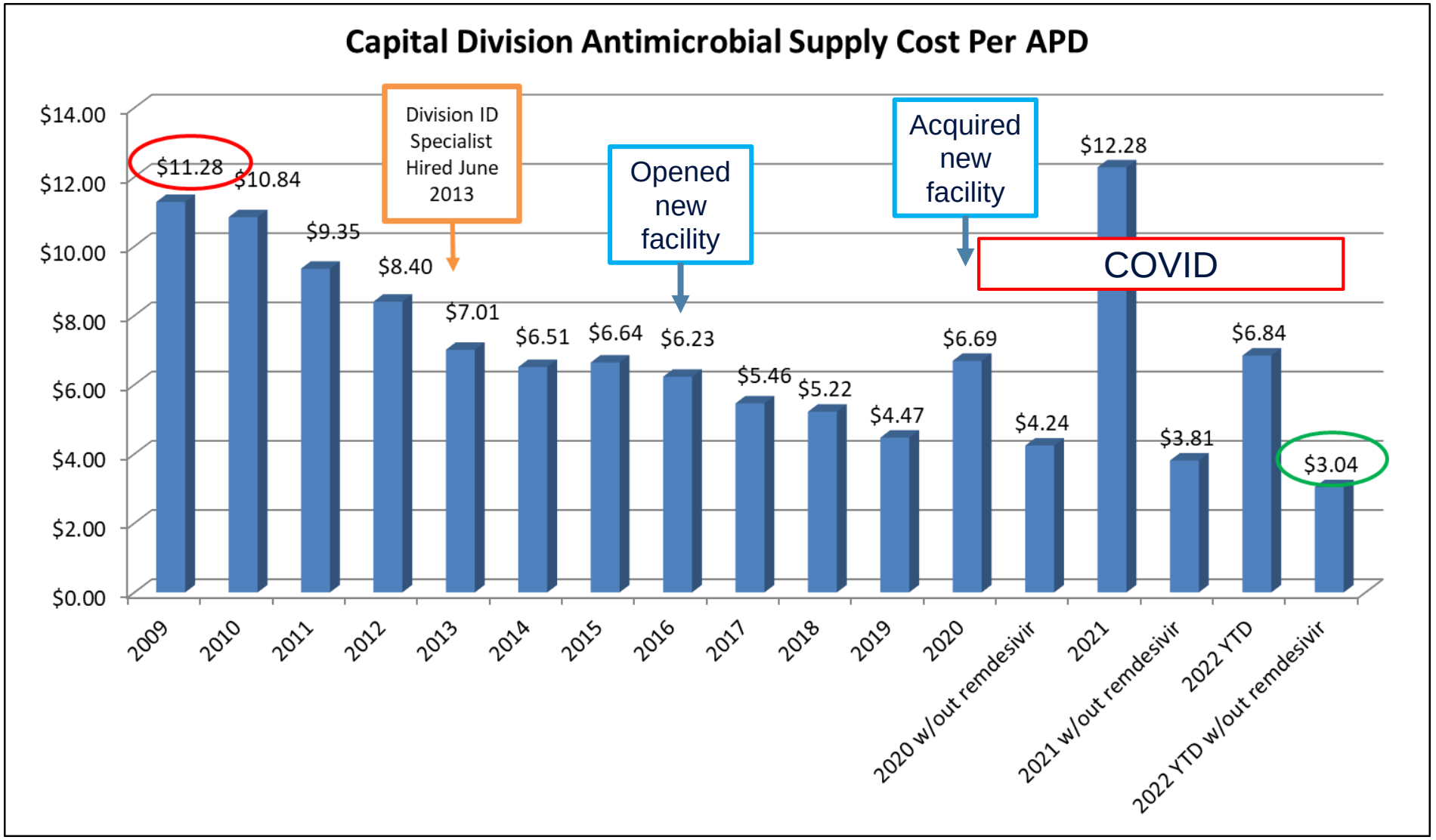
- Stratified by antimicrobial type, unit, and patient population (adult, pediatrics, NICU)
- Example: SAAR of 1.5 means antimicrobial use is 50% higher at institution versus similar facility



CDC. NHSN's Guide to the SAAR. November 2020. https://www.cdc.gov/nhsn/pdfs/ps-analysis-resources/aur/au-saar-guide-508.pdf. Accessed April 2022.

Antibiotic Use/Outcome Measures

Financial Impact



APD, adjusted patient days

Cumulative savings after implementing antimicrobial stewardship: $6 million

Cumulative savings with addition of ID pharmacist through 2019 (pre-COVID): $16 million

Cumulative savings with addition of ID pharmacist through 2021 (minus remdesivir):

$24.5 million in antimicrobial savings since addition of ID specialist covering 19 facilities

Novel & Non-Traditional Antimicrobial Stewardship Metrics

- Antibiotic Use Measures
  - Days of Antibiotic Spectrum Coverage
  - SAAR categories
- Outcome Measures
  - Avoidance of stewardship “never events”
    - Use of non-susceptible or unnecessarily broad agents after susceptibilities are known
    - Treatment of asymptomatic bacteriuria
    - Antibiotic use for viral upper respiratory tract infections
    - Prolonged postsurgical antibiotic prophylaxis
- Process Measures for Quality Improvement
  - Days of therapy avoided

Kakiuchi S et al. *Clin Infect Dis*. 2022. [epub ahead of print]
CDC. NHSN’s Guide to the SAAR. November 2020. https://www.cdc.gov/nhsn/pdfs/ps-analysis-resources/aur/au-saar-guide-508.pdf. Accessed April 2022.
Liu J et al. *Infect Control Hosp Epidemiol*. 2018;1-2.
Yarrington ME et al. *Curr Treat Options Infect Dis*. 2019;11:145-60.

Days of Antibiotic Spectrum Coverage

- Days of therapy metric does not take spectrum into consideration
- Days of antibiotic spectrum coverage assigns points to antibiotics based upon how many organism categories they cover:
  - Gram-negative:
    - *Escherichia coli/Klebsiella sp*
    - *Enterobacter/Citrobacter/Serratia sp*
    - *Pseudomonas aeruginosa*
    - *Acinetobacter baumannii*
  - Other:
    - Oral anaerobes
    - *Bacteroides fragilis*
    - Atypical organisms
    - *Moraxella/Haemophilus influenza*
  - Gram-positive:
    - *Staphylococcus aureus*
    - *Enterococcus sp*
    - *Streptococcus sp*
  - Coverage of resistance:
    - Extended-spectrum beta-lactamase (ESBL)
    - AmpC beta-lactamases
    - Methicillin-resistant *Staphylococcus aureus* (MRSA)
    - Vancomycin-resistant *Enterococcus* (VRE)
    - Multi-drug resistant organisms (MDRO)
    - Penicillin-resistant *Streptococcus pneumoniae* (PRSP)

Kakiuchi S et al. *Clin Infect Dis*. 2022. [epub ahead of print]

Days of Antibiotic Spectrum Coverage Examples

Ampicillin

- Gram-negative:
  - ***Escherichia coli****/Klebsiella sp*
  - *Enterobacter/Citrobacter/Serratia sp*
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*
- Other:
  - **Oral anaerobes**
  - *Bacteroides fragilis*
  - Atypical organisms
  - ***Moraxella/Haemophilus influenza***

- **Total score = 5**

- Gram-positive:
  - *Staphylococcus aureus*
  - ***Enterococcus sp***
  - ***Streptococcus sp***
- Coverage of resistance:
  - ESBL
  - AmpC
  - MRSA
  - VRE
  - MDRO
  - PRSP

Kakiuchi S et al. *Clin Infect Dis*. 2022. [epub ahead of print]

Days of Antibiotic Spectrum Coverage Examples

Linezolid

- Gram-negative:
  - *Escherichia coli/Klebsiella sp*
  - *Enterobacter/Citrobacter/Serratia sp*
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*
- Other:
  - Oral anaerobes
  - *Bacteroides fragilis*
  - Atypical organisms
  - *Moraxella/Haemophilus influenza*

- **Total score = 6**

- Gram-positive:
  - ***Staphylococcus aureus***
  - ***Enterococcus sp***
  - ***Streptococcus sp***
- Coverage of resistance:
  - ESBL
  - AmpC
  - **MRSA**
  - **VRE**
  - MDRO
  - **PRSP**

Kakiuchi S et al. *Clin Infect Dis*. 2022. [epub ahead of print]

Days of Antibiotic Spectrum Coverage vs. Days of Therapy

Scenario: 35-year-old male patient is admitted to the hospital with community-onset appendicitis with abscess, no significant past medical history or drug allergies

Antibiotic regimen	DOT/day	DASC/day	Cost
Piperacillin/tazobactam	1	11	$
Levofloxacin + metronidazole	2	14	$
Ceftriaxone + metronidazole	2	8	$
Ertapenem	1	9	$$
Meropenem	1	12	$
Tigecycline	1	15	$$$

Kakiuchi S et al. *Clin Infect Dis*. 2022. [epub ahead of print]
Solomkin JS et al. *Clin Infect Dis*. 2010;50(2):133-64.

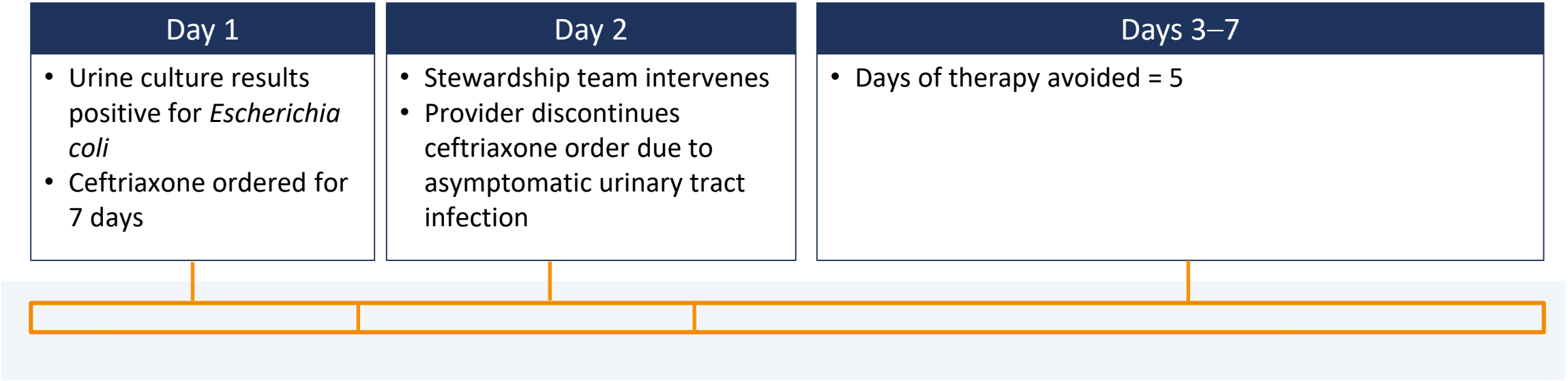
NHSN AU Option SAAR Categories

- Broad-spectrum antibacterial agents predominantly used for hospital-onset infections
- Broad-spectrum antibacterial agents predominantly used for community-acquired infections
- Antibacterial agents predominantly used for resistant gram-positive infections (e.g., MRSA)
- Narrow-spectrum beta-lactam agents
- Antifungal agents predominantly used for invasive candidiasis
- Antibacterial agents posing highest risk for *C. difficile* infection
- Additional options available for pediatric and neonatal populations

CDC. NHSN's Guide to the SAAR. November 2020. https://www.cdc.gov/nhsn/pdfs/ps-analysis-resources/aur/au-saar-guide-508.pdf. Accessed April 2022.

Days of Antimicrobial Therapy Avoided

- Reflects stewardship interventions to utilize shorter rather than traditional durations of therapy or avoidance of unnecessary treatment
- Makes assumptions on duration of therapy patient would have received without stewardship interventions
- Can lessen assumptions by only "counting" scenarios where antibiotics were ordered for a course and discontinued early due to stewardship team interventions



Datta S, et al. *J Hosp Med*. 2018;13(5):326-7.

What are the Best Metrics in Antimicrobial Stewardship?

Days of Therapy

Pros
- Most common AU metric
- Patient-level data
- Adjust for facility occupancy measures

Cons
- Does not account for renal doses
- May not measure efforts to promote narrow-spectrum agents
- Does not = length of therapy

Days of Antimicrobial Therapy Avoided

Pros
- Reflects interventions to decrease unnecessary AU
- Subset of prospective audit and feedback method
- Patient-level data

Cons
- Makes assumptions for number of days patients would have received without intervention
- Labor intensive
- Does not capture spectrum of AU

SAAR

Pros
- Standardized NHSN AU measure
- Risk-adjusted
- Benchmarking and comparisons
- Antibiotic groups and patient care locations

Cons
- Unable to get patient-level data
- Cannot inform AU appropriateness
- Predicted use based on AU from a previous year

Days of Antimicrobial Spectrum Coverage

Pros
- Prioritizes narrow-spectrum AU rather than single-agent
- Demonstrates results of de-escalation interventions
- More impactful in evaluating risk of MDRO development

Cons
- Requires additional steps to calculate from DOT
- Not commonly utilized
- Does not account for renal doses

AU, antimicrobial use; DOT, days of therapy; MDRO, multidrug-resistant organism; SAAR, standardized antimicrobial administration ratio

Assessment Question: #1 of 3

Which of the following metrics is a standardized NHSN measure of antimicrobial use but does not provide information on appropriateness of antimicrobial use?

a. Days of therapy

b. SAAR

c. Days of antibiotic spectrum coverage

d. Days of antimicrobial therapy avoided

Assessment Question: #1 of 3

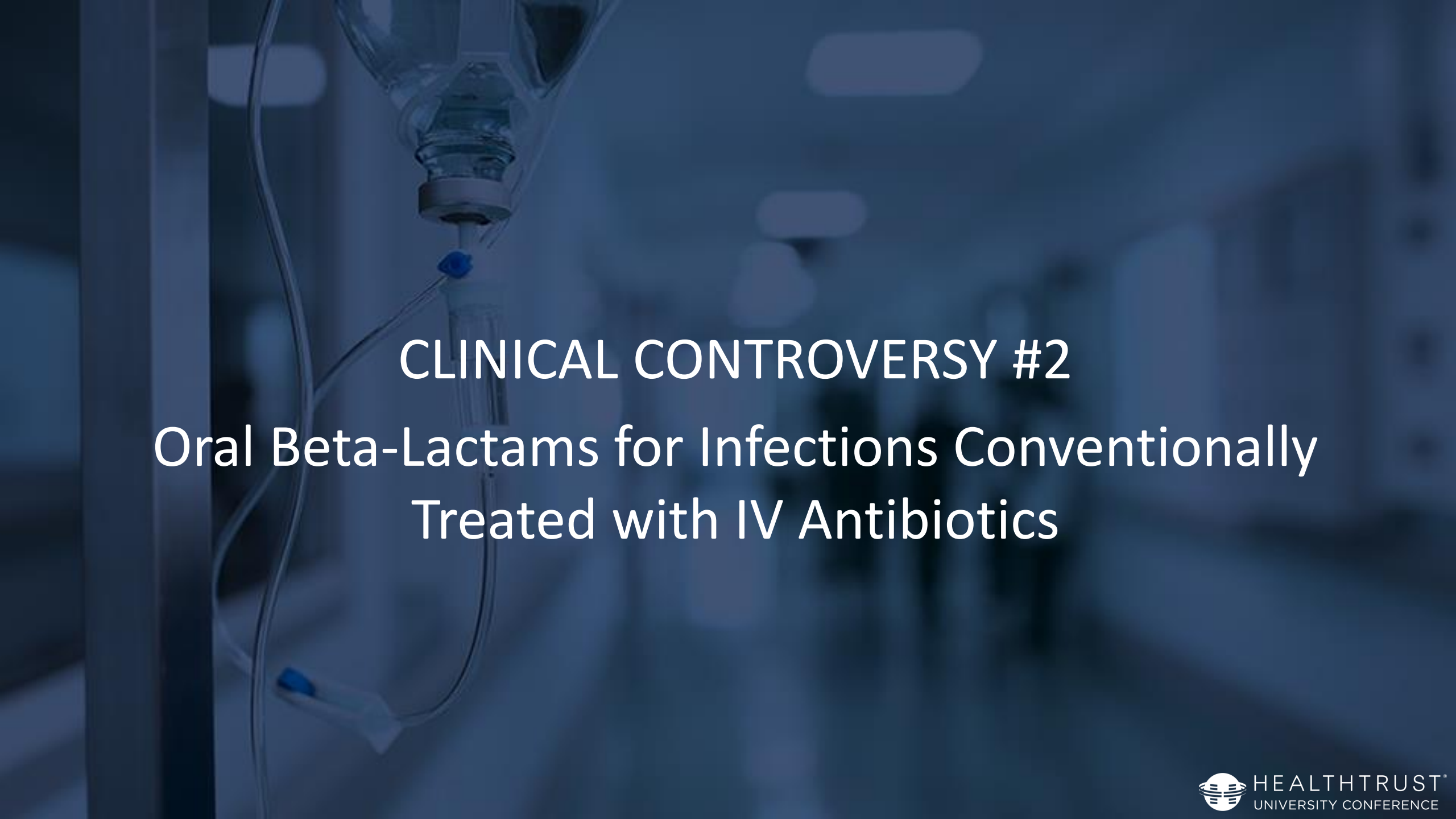
Which of the following metrics is a standardized NHSN measure of antimicrobial use but does not provide information on appropriateness of antimicrobial use?

a. Days of therapy

b. SAAR

c. Days of antibiotic spectrum coverage

d. Days of antimicrobial therapy avoided



CLINICAL CONTROVERSY #2

Oral Beta-Lactams for Infections Conventionally Treated with IV Antibiotics

ACCEPTED MANUSCRIPT

Early Switch from Intravenous to Oral Antibiotics in Skin- and Soft-tissue Infections: An Algorithm-based Prospective Multicentre Pilot Trial

Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

A Pathway for Community-Acquired Pneumonia With Rapid Conversion to Oral Therapy Improves Health Care Value

Efficacy of Early Oral Switch with β-Lactams for Low-Risk *Staphylococcus aureus* Bacteremia

Effectiveness of oral antibiotics for definitive therapy of Gram-negative bloodstream infections *

Leila F.
Helmut

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Evaluation of Partial Oral Antibiotic Treatment for Persons Who Inject Drugs and Are Hospitalized With Invasive

nfe

JAMA Network Open

Original Investigation | Infectious Diseases

Oral β-Lactam Antibiotics vs Fluoroquinolones or Trimethoprim-Sulfamethoxazole for Definitive Treatment of Enterobacterales Bacteremia From a Urine Source

Jesse D. Sutton, PharmD, MS; Vanessa W. Stevens, PhD; Nai-C

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Clinical Experience of Implementing Oral Versus Intravenous Antibiotics (OVIVA) in a Specialist Orthopedic Hospital

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibi Treatment of Endocarditis

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Association of 30-Day Mortality With Oral Step-Down vs Continued Intravenous Therapy in Patients Hospitalized With Enterobacteriaceae Bacteremia

Pranita D. Tamma, MD, MHS; Anna T. Conley, BA; Sara E. Cosgrove, MD, MS; Anthony D. Harris, MD, MPH; Ebbing Lautenbach, MD, MPH, MSCE; Joe Amoah, MD; Edina Avdic, PharmD, MBA; Pam Tolomeo, MPH; Jacqueleen Wise, BA; Sonia Subudhi, BA; Jennifer H. Han, MD, MSCE; for the Antibacterial Resistance Leadership Group

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Oral vs Intravenous Antibiotics for Patients With *Klebsiella pneumoniae* Liver Abscess: A Randomized, Controlled Noninferiority Study

Clinical considerations for oral beta-lactams as step-down therapy for Enterobacteriaceae bloodstream infections

Brya
Kufe

Retrospective analysis comparing oral stepdown therapy for enterobacteriaceae bloodstream infections: fluoroquinolones versus β-lactams

Nicholas J. Mercuro [a], Patricia Stogsdill [a,b],

Open Forum Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Oral Fluoroquinolone or Trimethoprim-Sulfamethoxazole vs ß-Lactams as Step-Down Therapy for Enterobacteriaceae Bacteremia: Systematic Review and Meta-analysis

Oral versus Intravenous Antibiotics for Bo and Joint Infection

RESEARCH ARTICLE

Oral beta-lactam step down in bacteremic *E. coli* urinary tract infections

Stephan Saad[1*], Neil Mina[2], Colin Lee[3] and Kevin Afra[4*]

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Concerns With Oral Beta-Lactams for Serious Infections

- Notoriously low bioavailability class
- Short half-lives require frequent dosing
- Based upon a %*f*T>MIC of at least 50% for penicillins and 60% for cephalosporins:

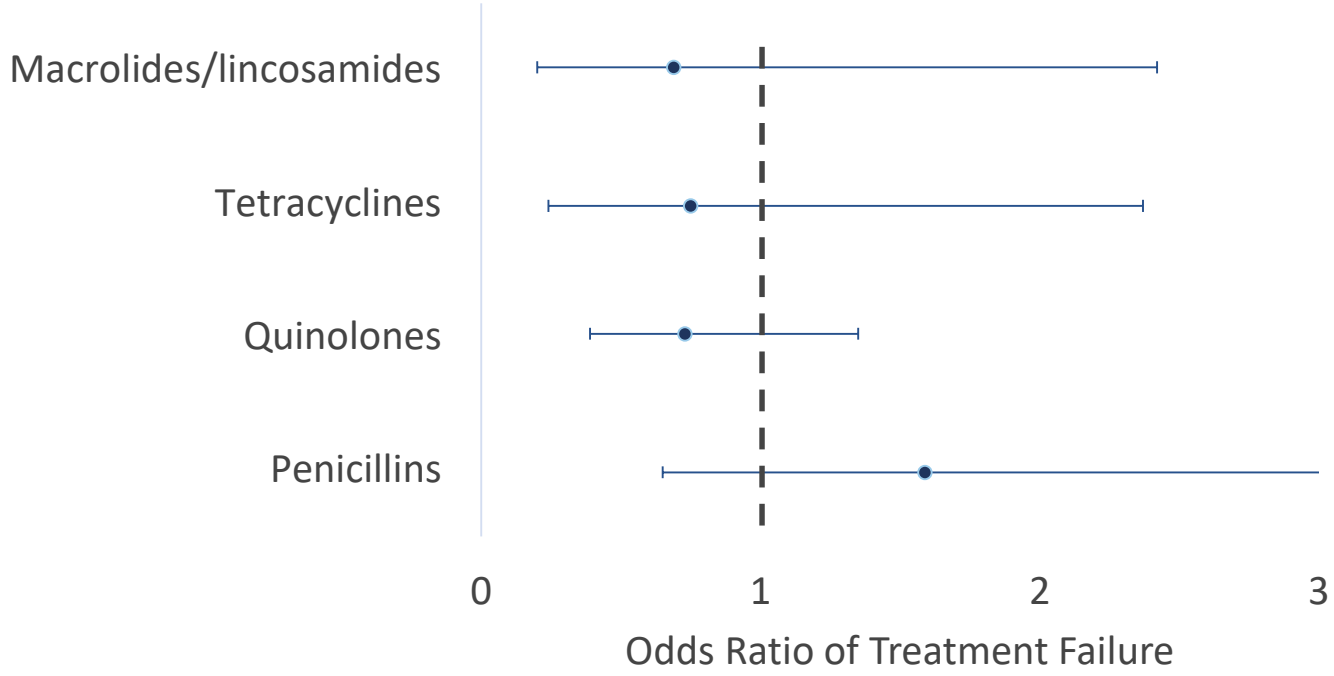
Antibiotic	Dose (mg)	Dosing interval (h)	%*f*T>MIC 8 mg/L	%*f*T>MIC 4 mg/L	%*f*T>MIC 2 mg/L	%*f*T>MIC 1 mg/L	CLSI breakpoint
Amoxicillin	1000	8	23.0	33.0	43.0	53.0	8
Cefdinir	300	12	-	-	-	7.4	1
Cefuroxime	500	12	-	0.4	10.2	20.5	4
Cefprozil	500	12	12.6	20.1	27.5	35.0	8

%*f*T>MIC: percentage of time free drug concentrations remain above minimum inhibitory concentration

Mogle BT et al. *Expert Opin Pharmacother*. 2019;20(8):903-7.
CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 32nd edition. CLSI guideline M100. Wayne,PA: Clinical and Laboratory Standards Institute; 2019.

Concerns With Oral Beta-Lactams for Serious Infections

- POET trial evaluating oral antibiotic use for endocarditis did not permit beta-lactam monotherapy
- OVIVA trial evaluating oral antibiotic use for osteomyelitis showed worse outcomes with beta-lactams compared to other antibiotics in a subgroup analysis



Iverson K et al. *N Eng J Med*. 2019;350(5):415-24.
Li HK et al. *N Eng J Med*. 2019;380(5):425-36.

Concerns With Oral Beta-Lactams for Serious Infections

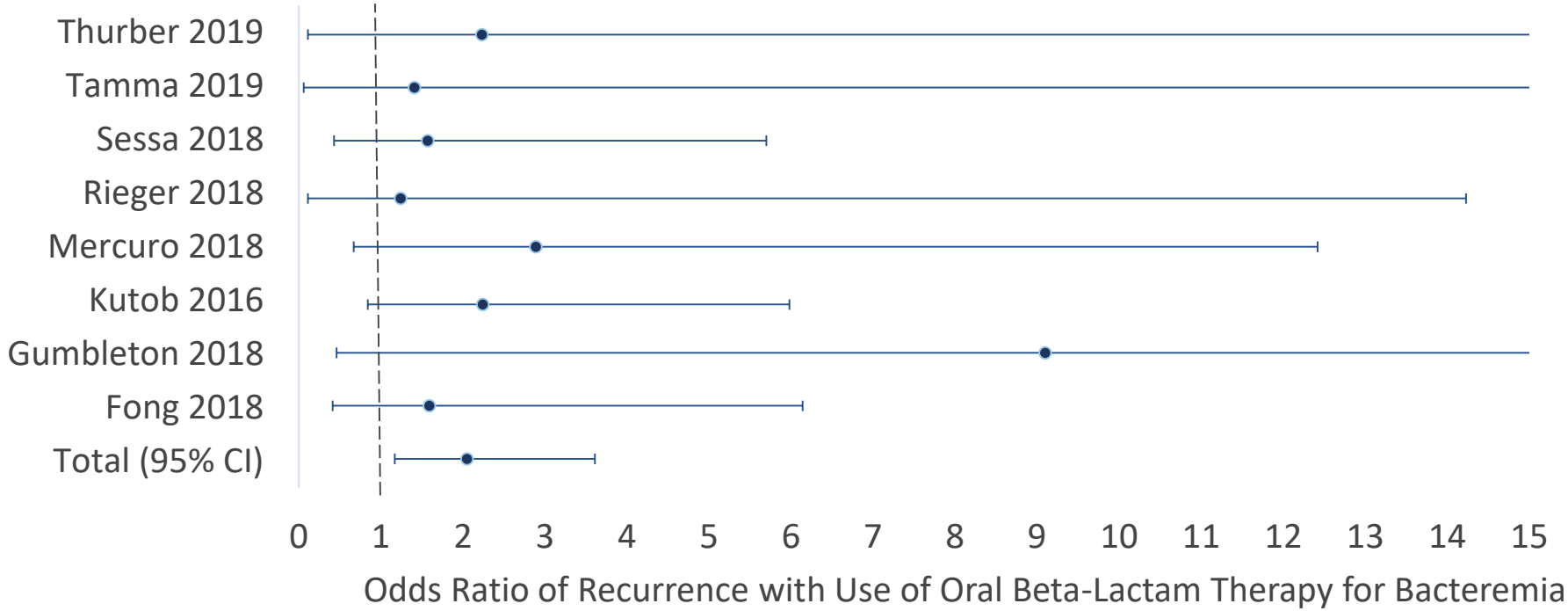
- Retrospective cohort study of oral regimens for gram-negative bacteremia

Bioavailability classification	High	Moderate	Low
Antibiotics	Levofloxacin	Ciprofloxacin or sulfamethoxazole/ trimethoprim	Beta-lactams
Incidence of treatment failure	2%	12%	14%
Hazard ratio of using a beta-lactam compared to levofloxacin	6.41 95% CI 1.65-42.03 p = 0.006		

Kutob LF et al. *Int J Antimicrob Agents*. 2016;48:498-503.

Concerns With Oral Beta-Lactams for Serious Infections

- Systematic review and meta-analysis of published data regarding oral therapy for bacteremias
  - No difference in mortality, but higher risk of recurrence in beta-lactam groups



- Consensus guidance on uncomplicated gram-negative bloodstream infections recommend fluoroquinolones or sulfamethoxazole/trimethoprim over beta-lactams

Punjabi C et al. *Open Forum Infect Dis*. 2019.
Heil EL et al. *Open Forum Infect Dis*. 2021.

Why Use an Oral Beta-Lactam for Serious Infections?

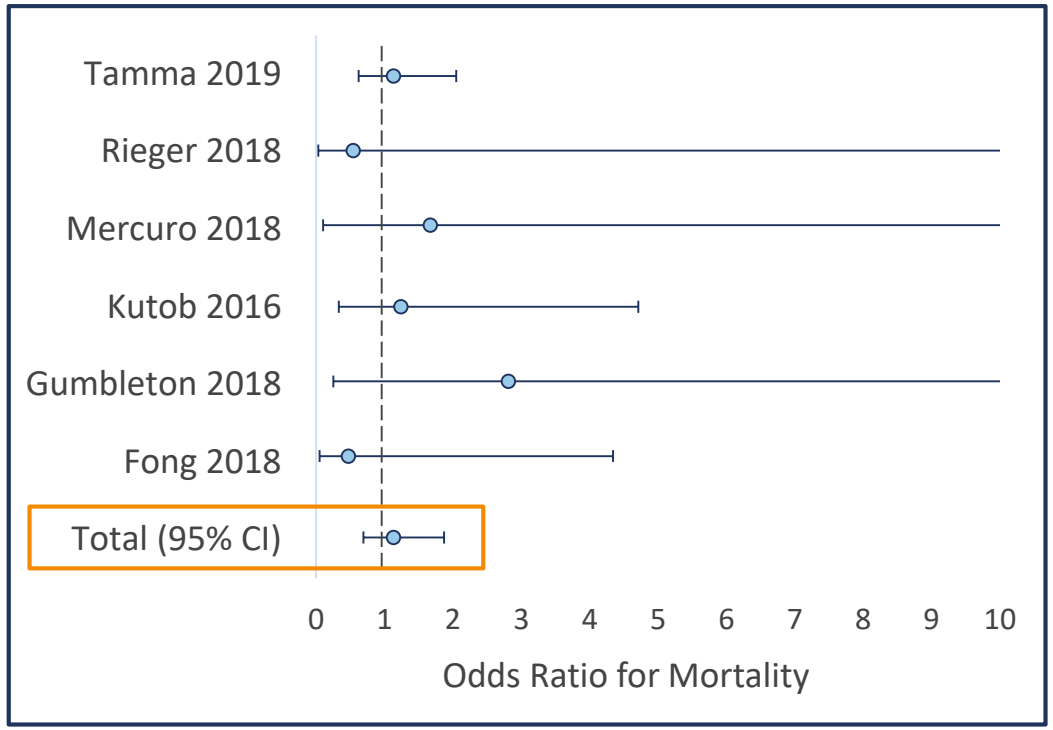
- Well-tolerated
- Good bacterial coverage
- Highly effective for many “uncomplicated” infections
- Pharmacokinetics – serum concentrations, tissue distribution, bioavailability
- Alternative oral antibiotic to fluoroquinolones
  - Multiple FDA warnings: tendinitis, tendon rupture, worsening myasthenia gravis symptoms, peripheral neuropathy, use for uncomplicated infections, hypoglycemia, mental health side effects
  - *C. difficile* risk 4 to 5 times greater than other antibiotics
  - Poor susceptibilities
  - Resistance development

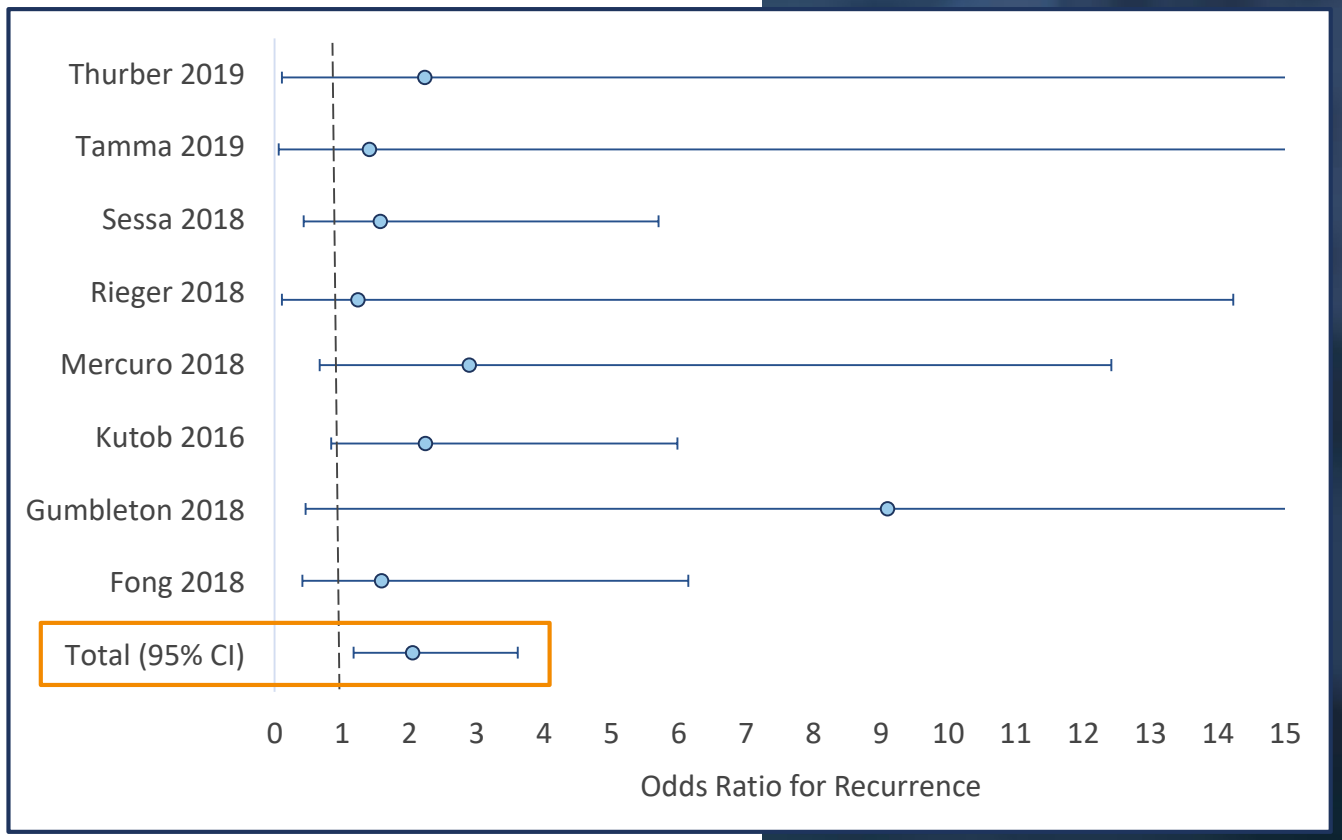
***C. difficile* colitis risk & antibiotic selection**	
Antibiotic	Risk Ratio
Tetracyclines	0.9
Sulfas and trimethoprim	1.8–1.9
Penicillin	1.9
Macrolides	1.5–2.7
Beta-lactamase combinations	2.3
1st and 2nd generation cephalosporins	2.4
3rd and 4th generation cephalosporins	3.1
Clindamycin	1.9–16.8
Fluoroquinolones	4–5.5

Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated *Clostridium difficile* infection. *Antimicrob Agents Chemother* 2013; 57(5): 2326-2332; Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of *Clostridium difficile* infection. *Clin Infect Dis* 2011; 53(1): 42-48.

Bacteremia – Oral Beta-Lactams vs. Fluoroquinolones & Trimethoprim/Sulfamethoxazole

No difference in all-cause mortality but increased risk for infection recurrence with oral beta-lactams – is this due to inadequate dosing?





Punjabi C, Tien V, Meng L, Deresinski S, Holubar M. Oral Fluoroquinolone or Trimethoprim-sulfamethoxazole vs. ß-lactams as Step-Down Therapy for Enterobacteriaceae Bacteremia: Systematic Review and Meta-analysis. *Open Forum Infect Dis*. 2019 Aug 14;6(10):ofz364.

Bacteremia & Oral Beta-Lactams – Use the Right Dose!

- Amoxicillin → 1000 mg every 8 hours
- Amoxicillin/clavulanate (amox/clav) → 875 mg every 8 hours
- Cephalexin → 1000 mg every 6 hours

Percentage of free time above the minimum inhibitory concentration (MIC) for various oral beta-lactams:

Antibiotic	Dose (mg)/ dosing interval (h)	%*f*T>MIC 8 mg/L	%*f*T>MIC 4 mg/L	%*f*T>MIC 2 mg/L	%*f*T>MIC 1 mg/L	%*f*T>MIC 0.5 mg/L	Maximum MIC allowing for target attainment	Highest frequency MIC for susceptible *E. coli*
Amoxicillin	500/8	13.0	23.0	33.0	43.0	53.0	0.5 mg/L	4 mg/L
Amoxicillin	1000/8	23.0	33.0	43.0	53.0	63.0	1 mg/L	4 mg/L
Amox/clav	875/12	11.0	17.6	24.3	31.0	37.6	--	4 mg/L
Amox/clav	875/8	16.4	26.4	36.4	46.4	56.4	0.5 mg/L	4 mg/L
Cephalexin	500/6	22.7	42.1	61.5	80.9	100	2 mg/L	4 mg/L
Cephalexin	1000/6	42.1	61.5	80.9	100	100	4 mg/L	4 mg/L

%*f*T>MIC: percentage of time free drug concentrations remain above minimum inhibitory concentration

Mogle BT, Beccari MV, Steele JM, Fazili T, Kufel WD. Clinical considerations for oral beta-lactams as step-down therapy for Enterobacteriaceae bloodstream infections. *Expert Opin Pharmacother*. 2019 Jun;20(8):903-907.

Endocarditis – Oral Step-Down Antibiotic Dosing Used in Published Clinical Studies

Drug	Organism	Dose
Amoxicillin	Sensitive streptococci or enterococci (for streptococci, with or without combination; and for enterococci, only in combination with rifampin, moxifloxacin, linezolid, or clindamycin)	1 gram 4 times daily
Dicloxacillin	Sensitive staphylococci (only in combination with rifampin)	1 gram 4 times daily
Levofloxacin	Sensitive staphylococci (only in combination with rifampin)	750 mg once daily
Moxifloxacin	Sensitive streptococci, enterococci, or staphylococci (only in combination with amoxicillin, rifampin, clindamycin, or linezolid)	400 mg once daily
Trimethoprim/sulfamethoxazole	Sensitive staphylococci	960 mg/4800 mg daily
Linezolid	For sensitive gram-positive cocci (for most patients in published studies, linezolid was used alone; in some studies, linezolid was given as a combination regimen with rifampin, moxifloxacin, clindamycin, or amoxicillin)	600 mg twice daily
Rifampin	Only as adjunctive agent (see above for other antibiotics rifampin has been combined with) and never as single agent	600 mg once or twice daily
Clindamycin	Only as adjunctive agent (see above for other antibiotics clindamycin has been combined with) and never as single agent	600 mg 3 times daily

Spellberg B, Chambers HF, Musher DM, Walsh TL, Bayer AS. Evaluation of a Paradigm Shift From Intravenous Antibiotics to Oral Step-Down Therapy for the Treatment of Infective Endocarditis: A Narrative Review. *JAMA Intern Med*. 2020 May 1;180(5):769-777.

Does Duration of Therapy or Source of Infection Make a Difference?

- Source of infection
  - Not found to be predictor of treatment outcome
  - Majority urine sources, source control, susceptible organism, able to take PO
  - POET (endocarditis) & OVIVA (osteomyelitis) included PO beta-lactams and no difference in outcomes between early-switch to PO versus continued IV therapy
- Duration of IV antibiotic before switch to PO antibiotic

	Tamma et al.	Kutob et al.	Mercuro et al.	Summary
Primary outcome	30-day mortality	Treatment failure	Clinical success	No Difference
< 3-5 days	13.1%	10%	86.7%	
> 3-5 days	13.4%	9%	87.5%	

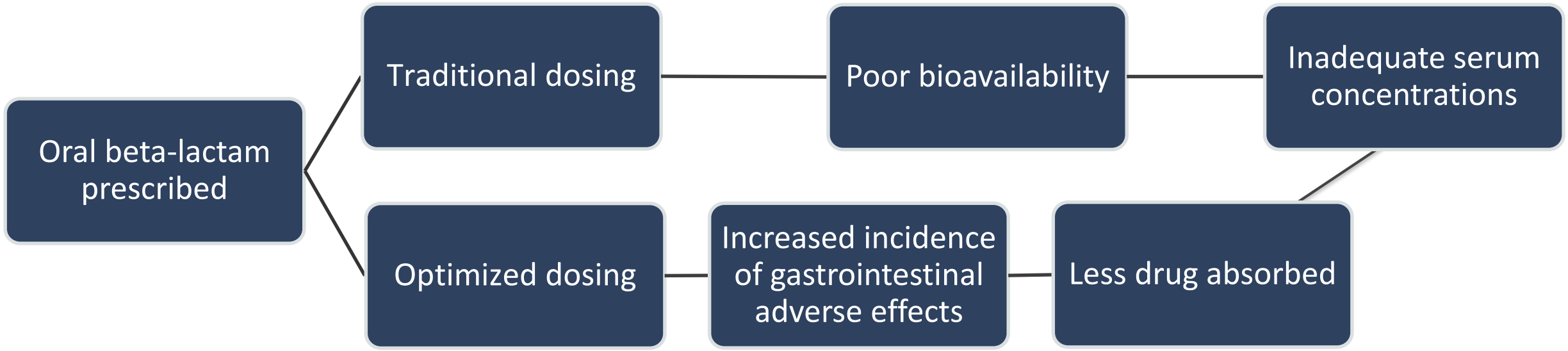
- Duration of total antibiotics
  - Clinical success – 7 to 10 days (88.2%) versus > 10 days (86.7%) of antibiotics
  - Other studies not specific to antibiotic type – similar efficacy in uncomplicated Gram-negative bacteremia

Bottom Line: Regardless of duration of IV antibiotics, duration of total antibiotics & source of infection, stepping down to a PO beta-lactam leads to similar outcomes as stepping down to a “high-bioavailable” PO antibiotic

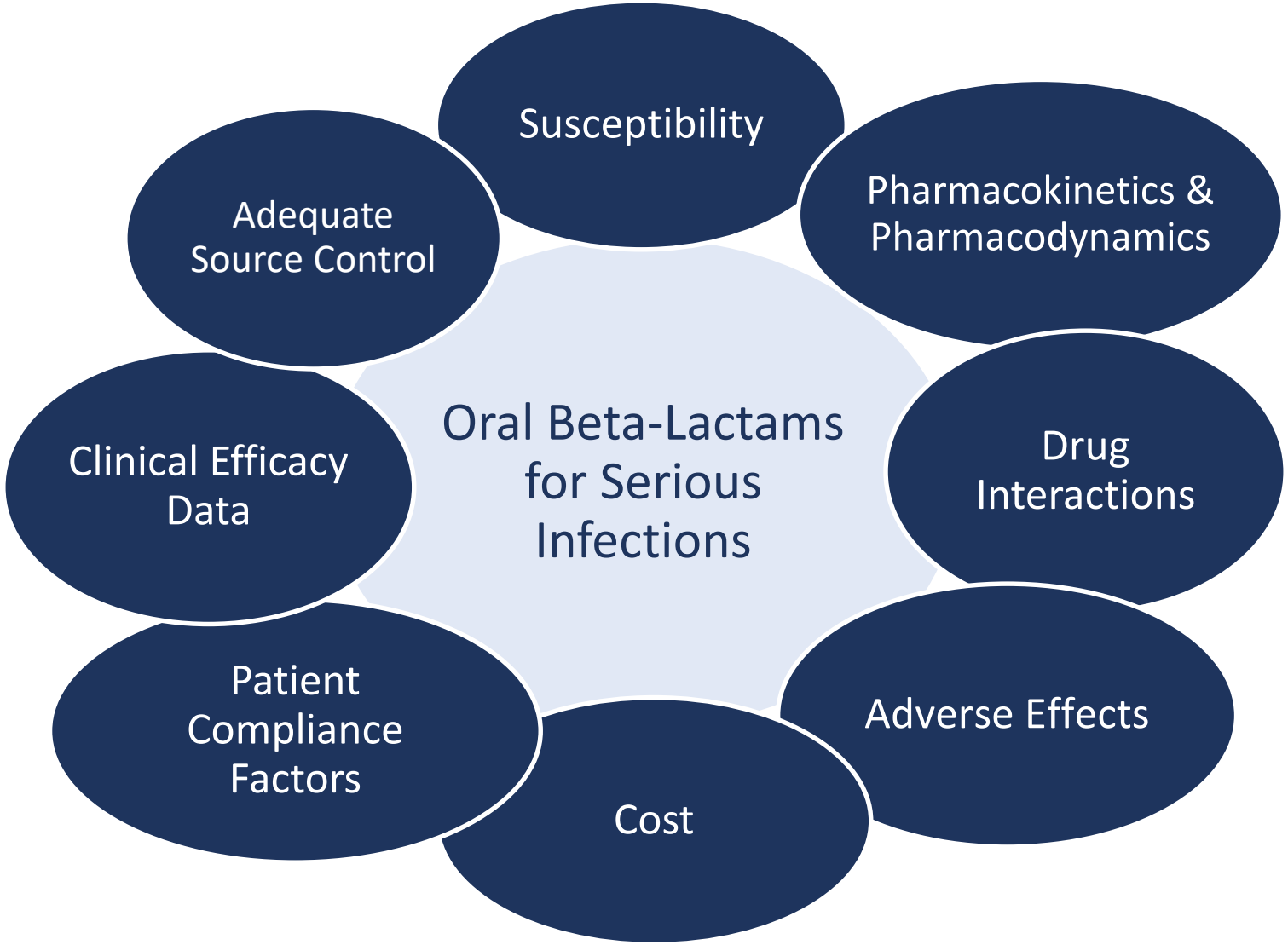
Iverson K et al. *N Eng J Med* 2019;350(5):415-24; Kutob LF et al. *Int J Antimicrob Agents* 2016;48(5):498-503; Li HK et al. *N Eng J Med* 2019;380(5):425-36; Mercuro NJ et al. *Int J Antimicrob Agents* 2018;51(5):687-92; Punjabi C, et al. *Open Forum Infect Dis* 2019;6(10):ofz364; Tamma PD et al. *JAMA Intern Med* 2019;179(3):316-23.

Concerns With Oral Beta-Lactams for Serious Infections

- Patients may not take medications at ideal intervals in ideal conditions
- Providers may not be aware of ideal dosing to make up for poor bioavailability
- Oral therapy results in less encounters with the healthcare team
- Less experience with oral beta-lactams for deep-seated infections
- Durations of therapy in studies supporting oral beta-lactams may be longer than necessary, creating falsely comparable results



Are We Ready to Use Oral Beta-Lactams for Serious Infections?



Seaton RA, Ritchie ND, Robb F, Stewart L, White B, Vallance C. From 'OPAT' to 'COpAT': implications of the OVIVA study for ambulatory management of bone and joint infection. *J Antimicrob Chemother*. 2019 Aug 1;74(8):2119-2121.

Assessment Question: #2 of 3

Which of the following should be considered when determining whether a patient with bacteremia is an appropriate candidate for oral beta-lactam therapy?

a. Susceptibility

b. Source control

c. Cost

d. Drug interactions

e. All of the above

Assessment Question: #2 of 3

Which of the following should be considered when determining whether a patient with bacteremia is an appropriate candidate for oral beta-lactam therapy?

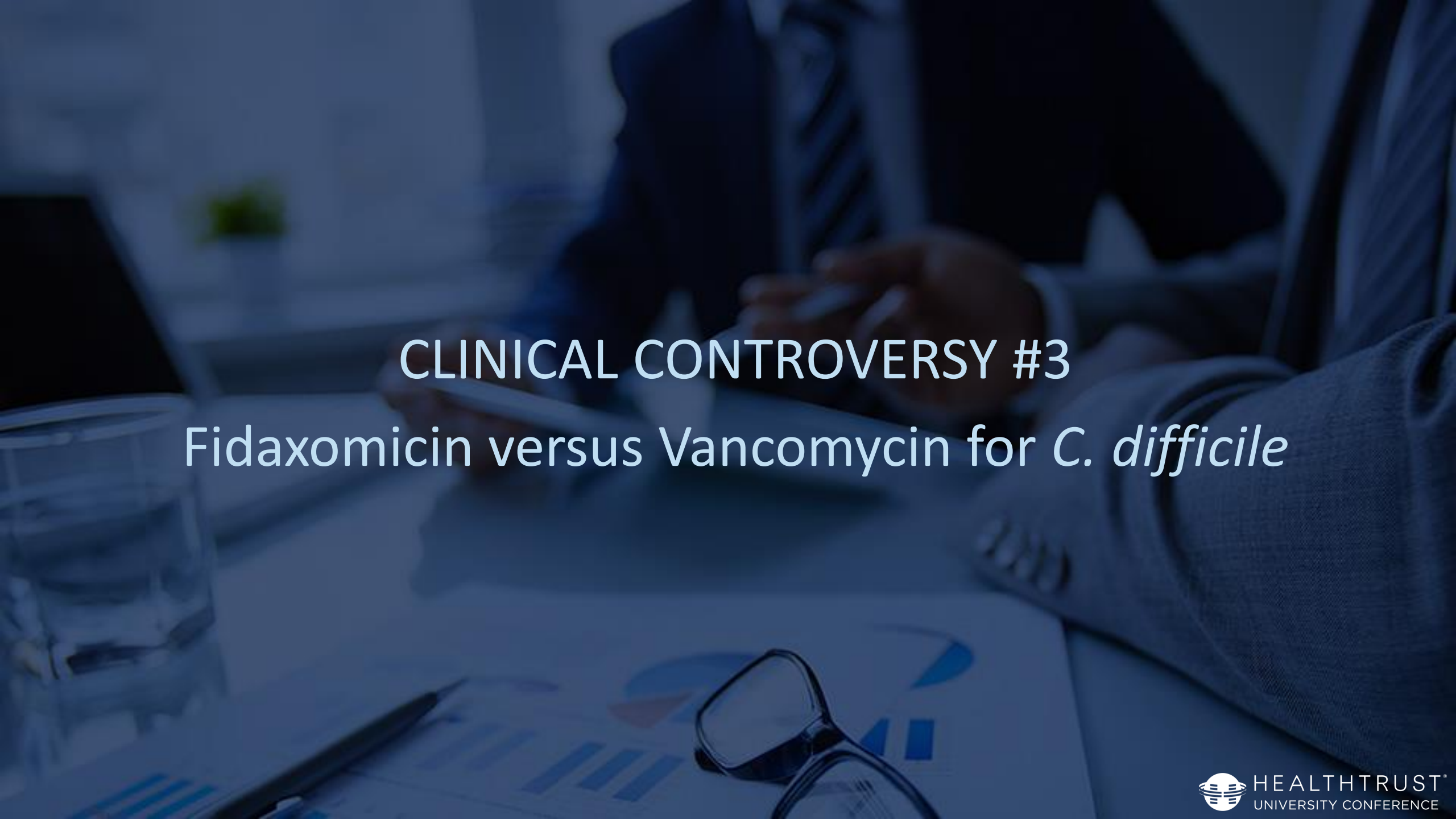
a. Susceptibility

b. Source control

c. Cost

d. Drug interactions

e. All of the above



CLINICAL CONTROVERSY #3

Fidaxomicin versus Vancomycin for *C. difficile*

Fidaxomicin Advantages

Fidaxomicin is better than oral vancomycin

- ✓ Minimal systemic absorption
- ✓ Narrow spectrum
- ✓ Highly active against *C. difficile*
- ✓ Resistance rarely reported
- ✓ Well-tolerated
- ✓ Twice daily dosing
- ✓ Similar efficacy for initial cure
- ✓ Lower risk of recurrent infections compared to oral vancomycin

Sustained response of *C. difficile* infection (follow-up 4 weeks)

Study	Fidaxomicin, Events/Total	Vancomycin, Events/Total	Risk Ratio (95% CI)
Louie 2011	214/287	198/309	1.16 (1.05, 1.30)
Cornely 2012	193/252	163/257	1.21 (1.08, 1.36)
Guery 2018	124/177	106/179	1.18 (1.01, 1.38)
Mikamo 2018	70/104	71/108	1.02 (0.85, 1.24)
Total (95% CI)	**601/820**	**538/853**	**1.16 (1.09, 1.24)**

Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021 Sep 7;73(5):e1029-e1044.

Fidaxomicin is Preferred in *C. difficile* Guideline Recommendations

Infectious Diseases Society of America (IDSA) & Society for Healthcare Epidemiology of America (SHEA) 2021 Guideline Update

- Initial *C. difficile* infection: Fidaxomicin suggested over standard course of vancomycin

"The use of fidaxomicin substantially improves desirable consequences (including a moderate increase in sustained resolution of CDI at four weeks, with comparable CDI initial clinical cure at end of therapy), while not increasing undesirable consequences…the balance favors the use of fidaxomicin rather than vancomycin in patients with an initial CDI episode."

- Recurrent *C. difficile* infection: Fidaxomicin suggested over other treatments (i.e. standard or tapered/pulsed course of vancomycin, rifaximin "chaser", and fecal microbiota transplant)

Source: Infectious Diseases Society of America (IDSA) & Society for Healthcare Epidemiology of America (SHEA) 2021 Guideline Update

Fidaxomicin is Preferred in *C. difficile* Guideline Recommendations

IDSA & SHEA 2021 Guidelines

- Initial *C. difficile* infection
  - Fidaxomicin suggested over standard course of vancomycin
- Recurrent *C. difficile* infection
  - Fidaxomicin suggested over other treatments (i.e., standard or tapered/pulsed course of vancomycin, rifaximin “chaser” and fecal microbiota transplant)

American College of Gastroenterology (ACG) 2021 Guidelines

- Initial *C. difficile* infection
  - Fidaxomicin or vancomycin
- Recurrent *C. difficile* infection
  - Fidaxomicin in those given vancomycin or metronidazole for initial infection
  - Tapered/pulsed course of vancomycin is recommended option in those given fidaxomicin, vancomycin or metronidazole for initial infection

Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021 Sep 7;73(5):e1029-e1044.

Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. Am J Gastroenterol. 2021 Jun 1;116(6):1124-1147.

Fidaxomicin Is Only "Suggested" by IDSA & Vanco Is Equivalent First-Line Option by ACG

IDSA & SHEA 2021 Guidelines

- Initial *C. difficile* infection
  - Fidaxomicin suggested over standard course of vancomycin
    - **Vancomycin acceptable alternative**
- Recurrent *C. difficile* infection
  - Fidaxomicin suggested over other treatments (i.e. standard or tapered/pulsed course of vancomycin, rifaximin "chaser" and fecal microbiota transplant)

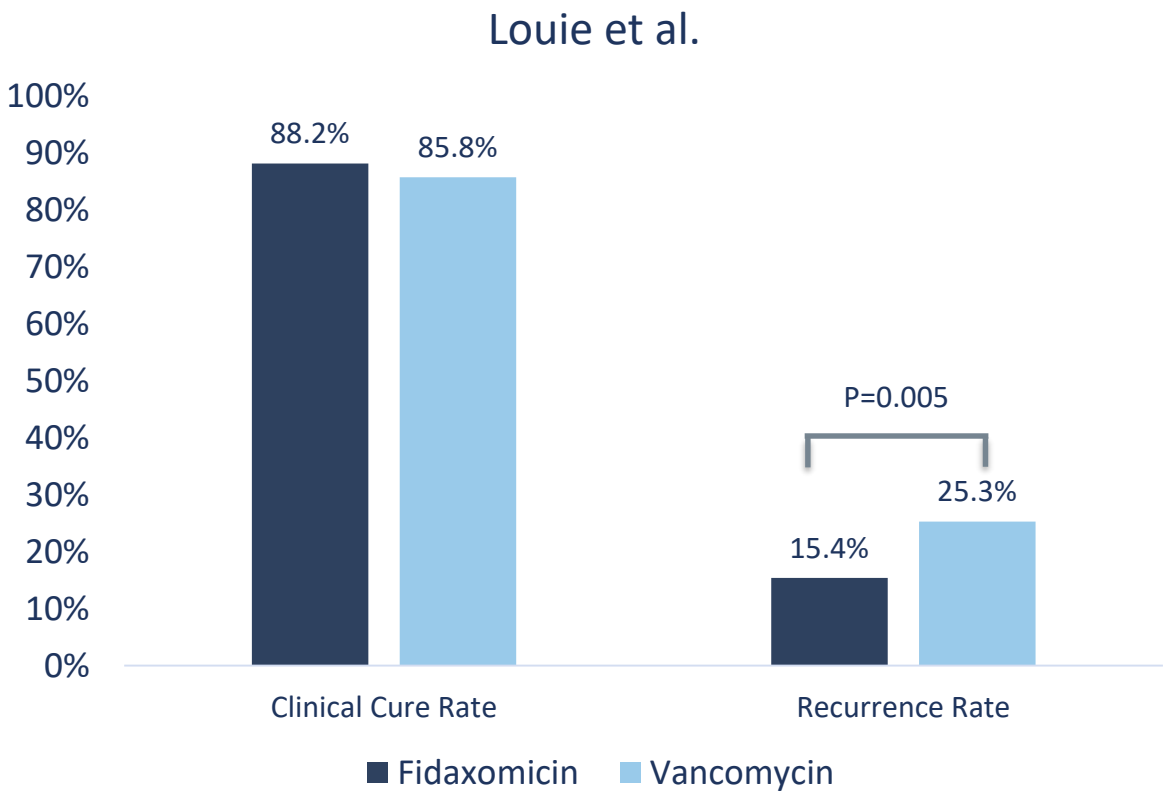
Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021 Sep 7;73(5):e1029-e1044.

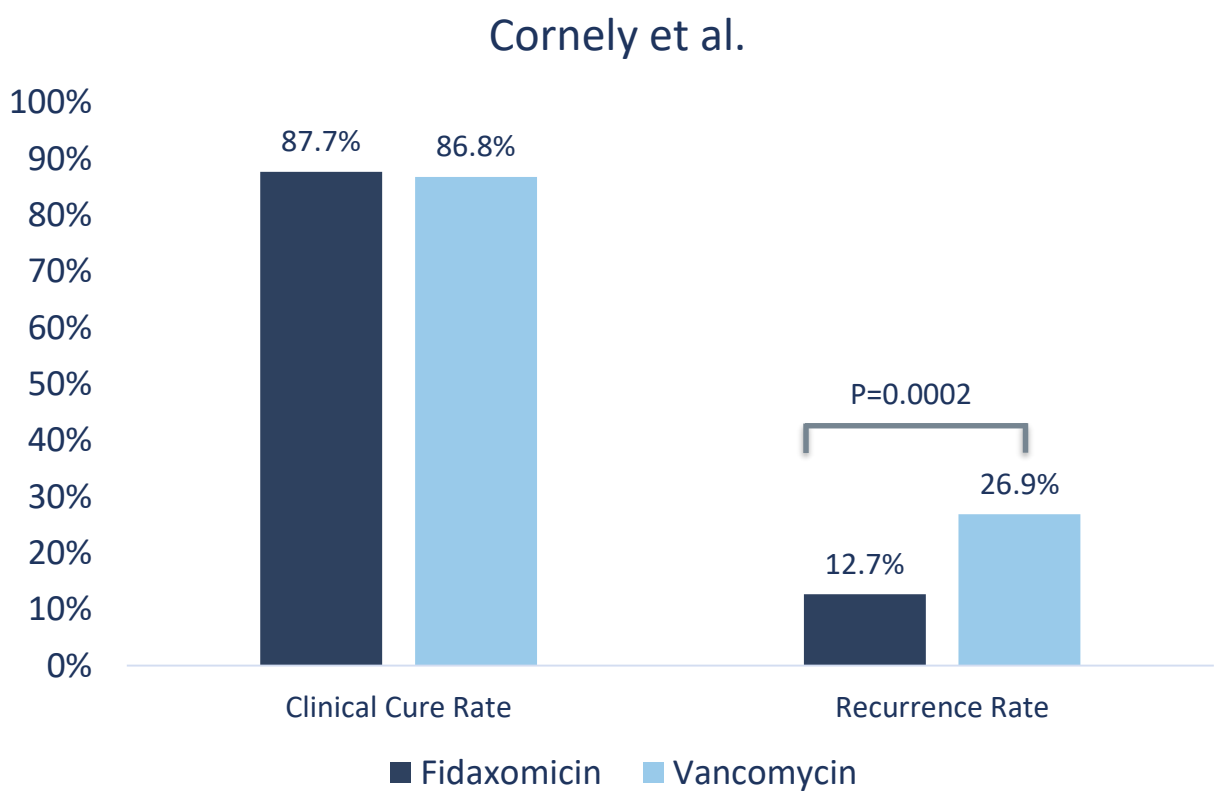
American College of Gastroenterology (ACG) 2021 Guidelines

- Initial *C. difficile* infection
  - Fidaxomicin or vancomycin
    - **Although vancomycin is less expensive, lower recurrence rates of fidaxomicin imply overall similar cost-effectiveness of both agents**
- Recurrent *C. difficile* infection
  - Fidaxomicin in those given vancomycin or metronidazole for initial infection
  - Tapered/pulsed course of vancomycin is recommended option in those given fidaxomicin, vancomycin or metronidazole for initial infection

Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. Am J Gastroenterol. 2021 Jun 1;116(6):1124-1147.

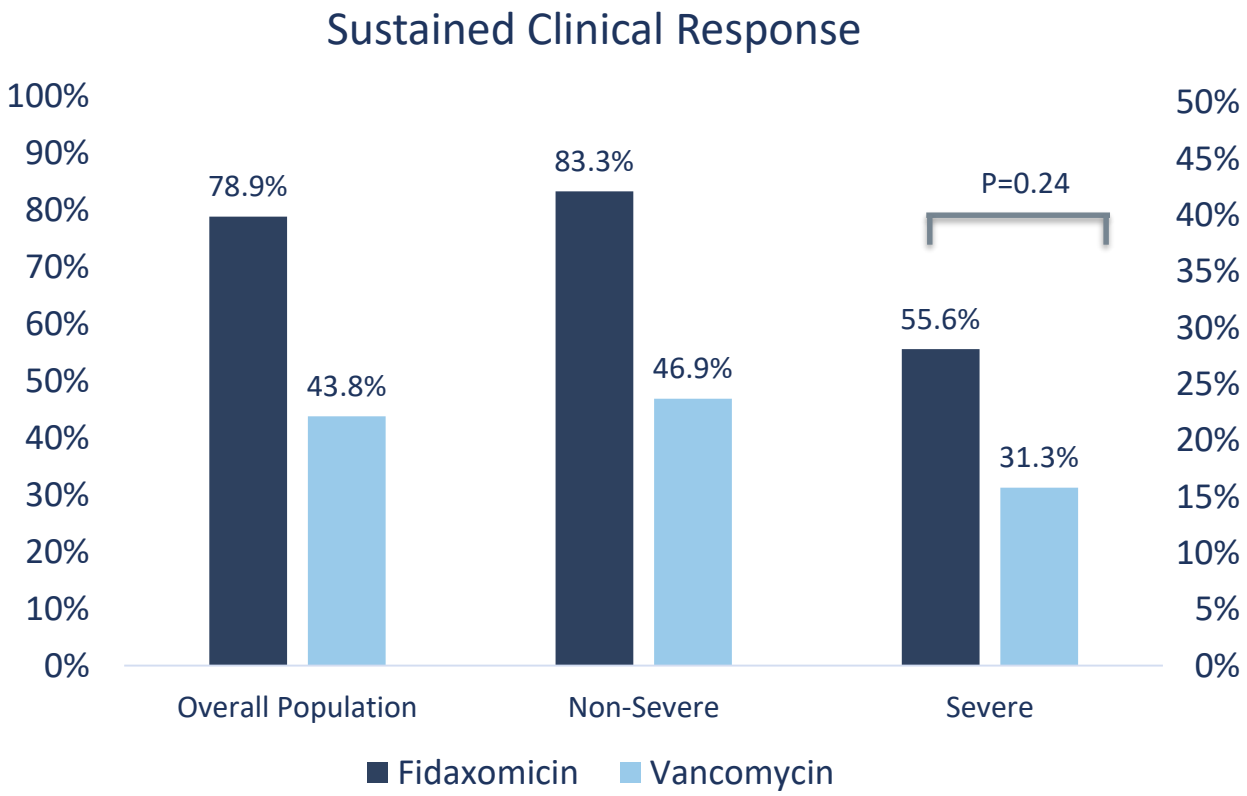
Vancomycin Compared to Fidaxomicin

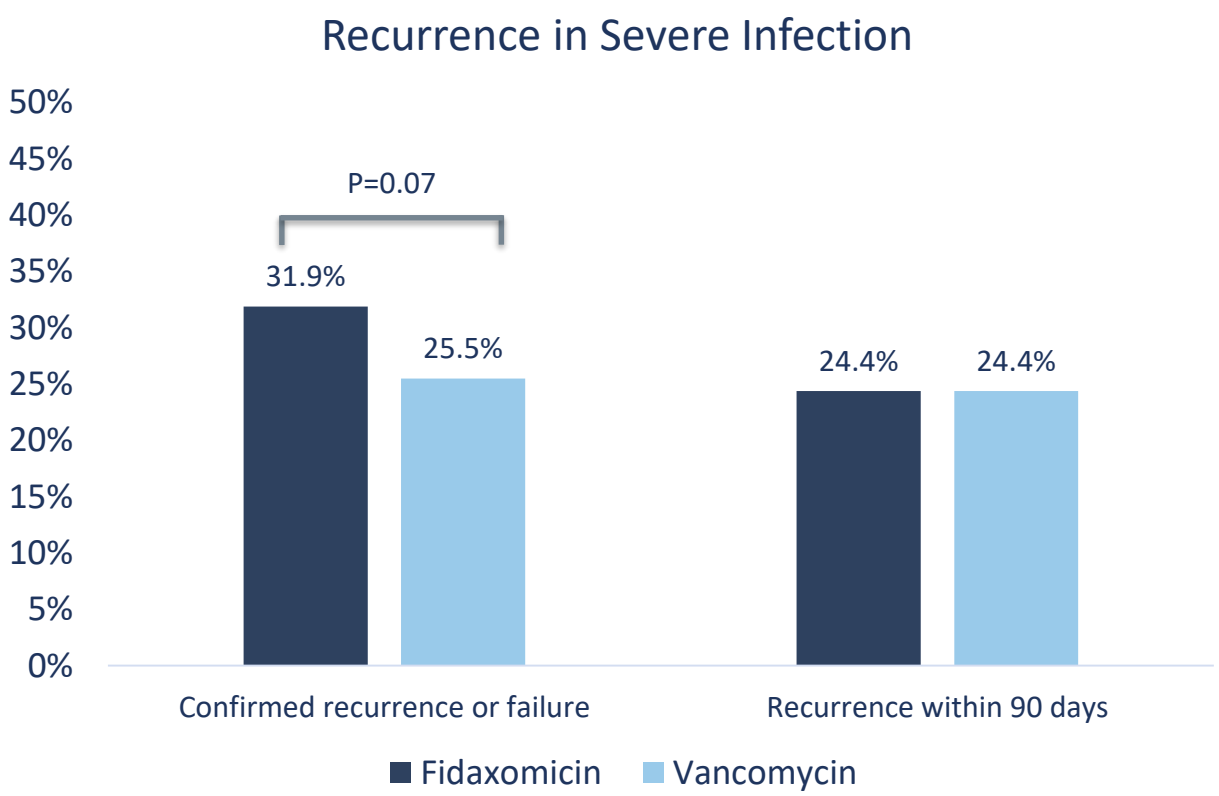




Louie TJ et al. *N Engl J Med*. 2011;364:422-31.
Cornely OA et al. *Lancet Infect Dis*. 2012;12:281-9.

Vancomycin Compared to Fidaxomicin: Severe Infections





Polivkova S et al. *Int J Infect Dis*. 2021;103:226-33.
Gentry CA et al. *Clin Microbiol Infect*. 2019;25:987-93.

HEALTHTRUST UNIVERSITY CONFERENCE

Vancomycin Compared to Fidaxomicin: Concomitant Antibiotic Use

Pooled data from two studies evaluating incidence of *Clostridioides difficile* infection recurrence when concomitant antibiotics were used

	Fidaxomicin	Vancomycin	p-value
No concomitant antibiotic	11.9%	23.1%	< 0.001
Any concomitant antibiotic	16.9%	29.2%	0.048
High-risk concomitant antibiotic*	23.9%	29.4%	**0.54**

*High-risk concomitant antibiotic defined as:

- 2nd generation cephalosporin
- 3rd generation cephalosporin
- 4th generation cephalosporin
- Carbapenem
- Fluoroquinolone
- Clindamycin

Mullane K et al. *Clin Infect Dis.* 2011;53(5):440-447.

Vancomycin Take Home Points

Vancomycin is a more cost-effective treatment of an initial infection with *Clostridioides difficile*

Fidaxomicin won't provide benefit over vancomycin for all patients with *Clostridioides difficile* infection

Least effective medication is one that's not taken

Preservation of novel antimicrobial therapies for patients who require them

Oral Vancomycin vs. Fidaxomicin for Initial *C. difficile* Infection

- Are some patients more likely to benefit from fidaxomicin for initial treatment?
- Risk factors for recurrence:
  - Age ≥ 65 years
  - Immunocompromised
  - Severe *C. difficile* infection*
  - Ribotype 027/078/244**
  - History of prior *C. difficile* infection
- Do oral vancomycin and fidaxomicin perform equally well in real-world settings?
  - Consider evaluating recurrences in your *C. difficile* patients and adjusting/stratifying by risk factors for recurrence
  - If possible, determine most common ribotypes in your patients – if predominantly 027, fidaxomicin may not provide an advantage over oral vancomycin for initial infection

These subgroups have not been adequately studied in randomized controlled trials

- *Fidaxomicin may not provide benefit over vancomycin in severe infection
- **Fidaxomicin had no advantage in patients with 027 ribotype

Assessment Question: #3 of 3

Which of the following is true regarding clinical efficacy data comparing fidaxomicin to vancomycin for treatment of C. difficile *infection?*

a. Fidaxomicin has higher initial clinical cure

b. Fidaxomicin is associated with lower recurrences

c. Fidaxomicin is more beneficial in patients with severe *C. difficile*

d. Fidaxomicin is more beneficial in patients with the 027 ribotype

e. All of the above

Assessment Question: #3 of 3

Which of the following is true regarding clinical efficacy data comparing fidaxomicin to vancomycin for treatment of C. difficile *infection?*

a. Fidaxomicin has higher initial clinical cure

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d. Fidaxomicin is more beneficial in patients with the 027 ribotype

e. All of the above

Conclusion & Summary

Antimicrobial Stewardship Metrics

- Days of therapy (DOT) and the Standardized Antimicrobial Administration Ratio (SAAR) are widely used and standard antimicrobial use metrics are recommended to measure improvements and/or opportunities
- Novel stewardship metrics, such as SAAR subcategories, days of antimicrobial spectrum, or days of therapy avoided may more accurately reflect stewardship interventions to utilize narrower spectrum agents and shorter durations of therapy

Oral Beta-Lactams for Infections Conventionally Treated With IV Antibiotics

- Emerging data suggests oral beta-lactams may have equivalent efficacy versus “high-bioavailable” antibiotics for serious infections
- If an oral beta-lactam is considered, there are several important variables to consider on a case-by-case basis

Conclusion & Summary, continued

Fidaxomicin versus Vancomycin for *C. difficile* Infection

- Recent guidelines have discrepant recommendations on preferred therapy for an initial *C. difficile* infection
- Vancomycin should remain an acceptable first-line option for most patients
- Consider evaluating facility-specific outcomes with fidaxomicin versus vancomycin for initial infection

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Thank you…

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