Antimicrobial Stewardship for the Practicing Clinician

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Nothing to Disclose

What *IS* Antimicrobial Stewardship??

- Defined by IDSA and SHEA as "…coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal drug regimen including dosing, duration of therapy, and route of administration."

- Think of it as maximizing the appropriateness of antimicrobial regimens
  - Are patients receiving appropriately narrow (or broad) therapy?
  - Are they receiving the correct dose for their renal function or indication?
  - Is the proposed duration of therapy correct?
  - If on IV therapy, is it possible, or when would it be possible to transition the patient to PO therapy?

BUT…This Isn’t What We’re Talking About Today

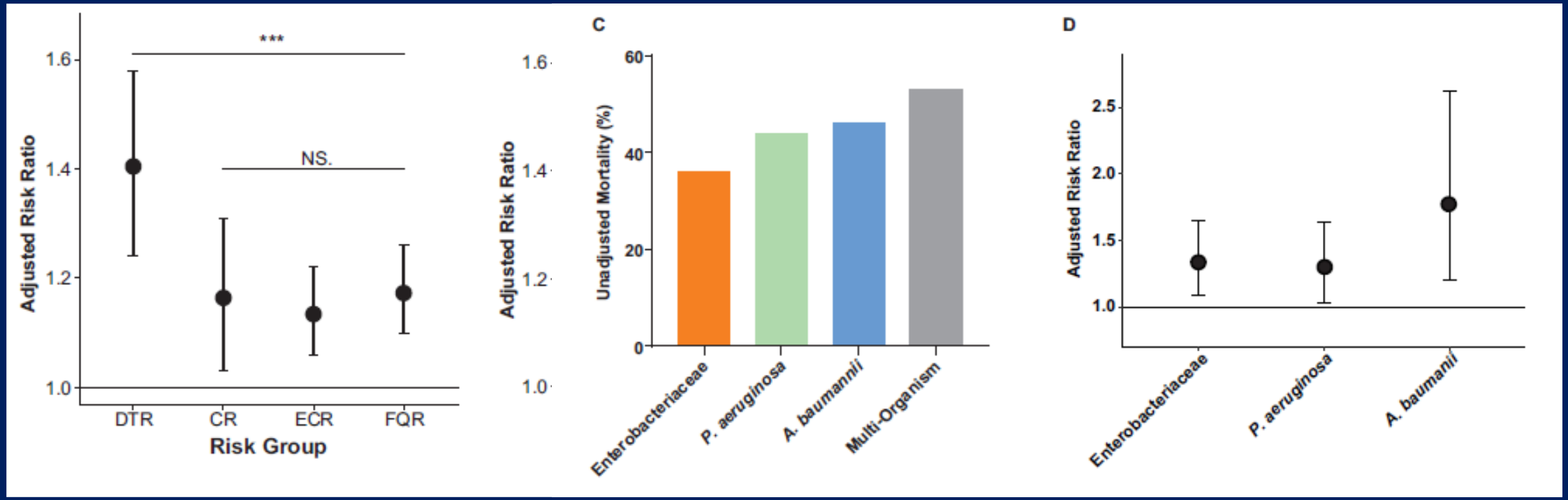
- Every provider that prescribes antimicrobials has a role to play in antimicrobial stewardship
- Even if you’re not on your institution's ASP or P&T committee you can look for ways in your daily practice to impact stewardship
- And inappropriate antibiotic use affects us all…

DTR in Gram-negative Bacteremia at 173 US Hospitals

Unadjusted Mortality in DTR = 43%

Risk Factors Associated with a DTR:

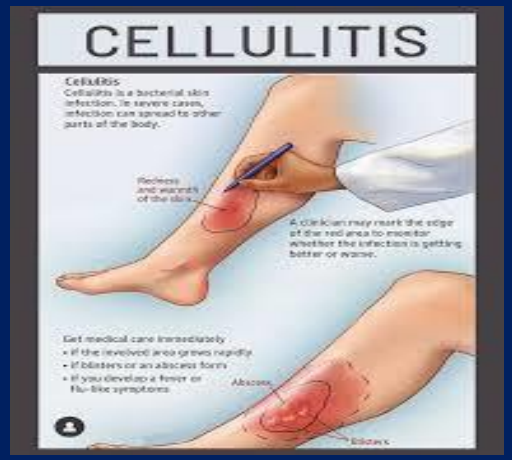
- HAI: 1.83 (95% CI 1.45-2.30)
- Prior BSI: 1.77 (95% CI 1.34-2.34)



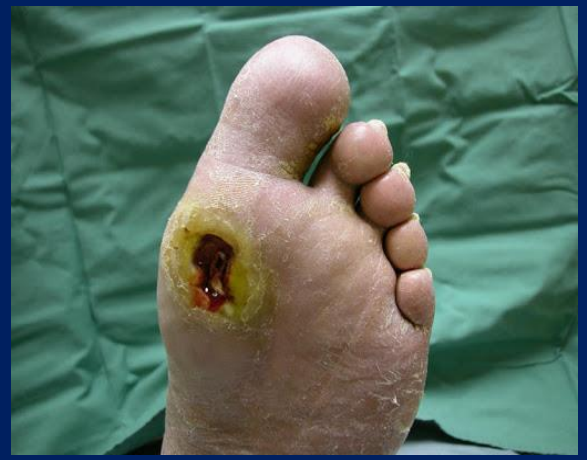
Kadri et al. *Clin Infect Dis* 2018; 67: 1803-14.

Focus Area:
Therapy De-Escalation & Duration of Treatment

Pneumonia



Cellulitis



Diabetic Foot Infections

Focus Area: Antimicrobial Dosing

First Focus Area:

Pneumonia

Pneumonia: CAP – 2019 Updated Guidelines

Recommendation	2007 ATS/IDSA Guideline	2019 ATS/IDSA Guideline
Sputum culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or *Pseudomonas aeruginosa*
Blood culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or *P. aeruginosa*
Macrolide monotherapy	Strong recommendation for outpatients	Conditional recommendation for outpatients based on resistance levels
Use of procalcitonin	Not covered	Not recommended to determine need for initial antibacterial therapy
Use of corticosteroids	Not covered	Recommended not to use. May be considered in patients with refractory septic shock
Use of healthcare-associated pneumonia category	Accepted as introduced in the 2005 ATS/IDSA hospital-acquired and ventilator-associated pneumonia guidelines	Recommend abandoning this categorization. Emphasis on local epidemiology and validated risk factors to determine need for MRSA or *P. aeruginosa* coverage. Increased emphasis on deescalation of treatment if cultures are negative
Standard empiric therapy for severe CAP	β-Lactam/macrolide and β-lactam/fluoroquinolone combinations given equal weighting	Both accepted but stronger evidence in favor of β-lactam/macrolide combination
Routine use of follow-up chest imaging	Not addressed	Recommended not to obtain. Patients may be eligible for lung cancer screening, which should be performed as clinically indicated

Definition of abbreviations: ATS = American Thoracic Society; CAP = community-acquired pneumonia; IDSA = Infectious Diseases Society of America; MRSA = methicillin-resistant *Staphylococcus aureus*.

Metlay et al. *Am J Resp Crit Care Med* 2019; 200: e45-67.

CAP Treatment Recommendations

Outpatient Treatment	
No comorbidities or risk factors for MRSA or *Pseudomonas*	Amoxicillin or Doxycycline or Macrolide (if local pneumococcal resistance is <25%)
With comorbidities	Amoxicillin/clavulanate or a cephalosporin PLUS Macrolide or doxycycline OR Monotherapy with a respiratory fluoroquinolone
Inpatient Treatment	
Non-severe disease	Beta-lactam + macrolide OR Respiratory fluoroquinolone
Severe disease	Beta-lactam + macrolide OR Beta-lactam + respiratory fluoroquinolone

Metlay et al. *Am J Resp Crit Care Med* 2019; 200: e45-67.

When to Consider MRSA or *Pseudomonas* Coverage

Inpatient Treatment			
	Prior Respiratory Isolation of MRSA	Prior Respiratory Isolation of *Pseudomonas*	Recent Hospitalizations and Parenteral Antibiotics and Locally Validated Risk Factors for MRSA
Non-severe disease	Add MRSA coverage and obtain cultures/nasal PCR to allow for de-escalation or need for continued therapy	Add Pseudomonal coverage and obtain cultures to allow for de-escalation or need for continued therapy	Obtain cultures BUT withhold unless cultures are positive
Severe disease	Add MRSA coverage and obtain cultures/nasal PCR to allow for de-escalation or need for continued therapy	Add Pseudomonal coverage and obtain cultures to allow for de-escalation or need for continued therapy	Add MRSA coverage and obtain cultures/nasal PCR to allow for de-escalation or need for continued therapy

Metlay et al. *Am J Resp Crit Care Med* 2019; 200: e45-67.

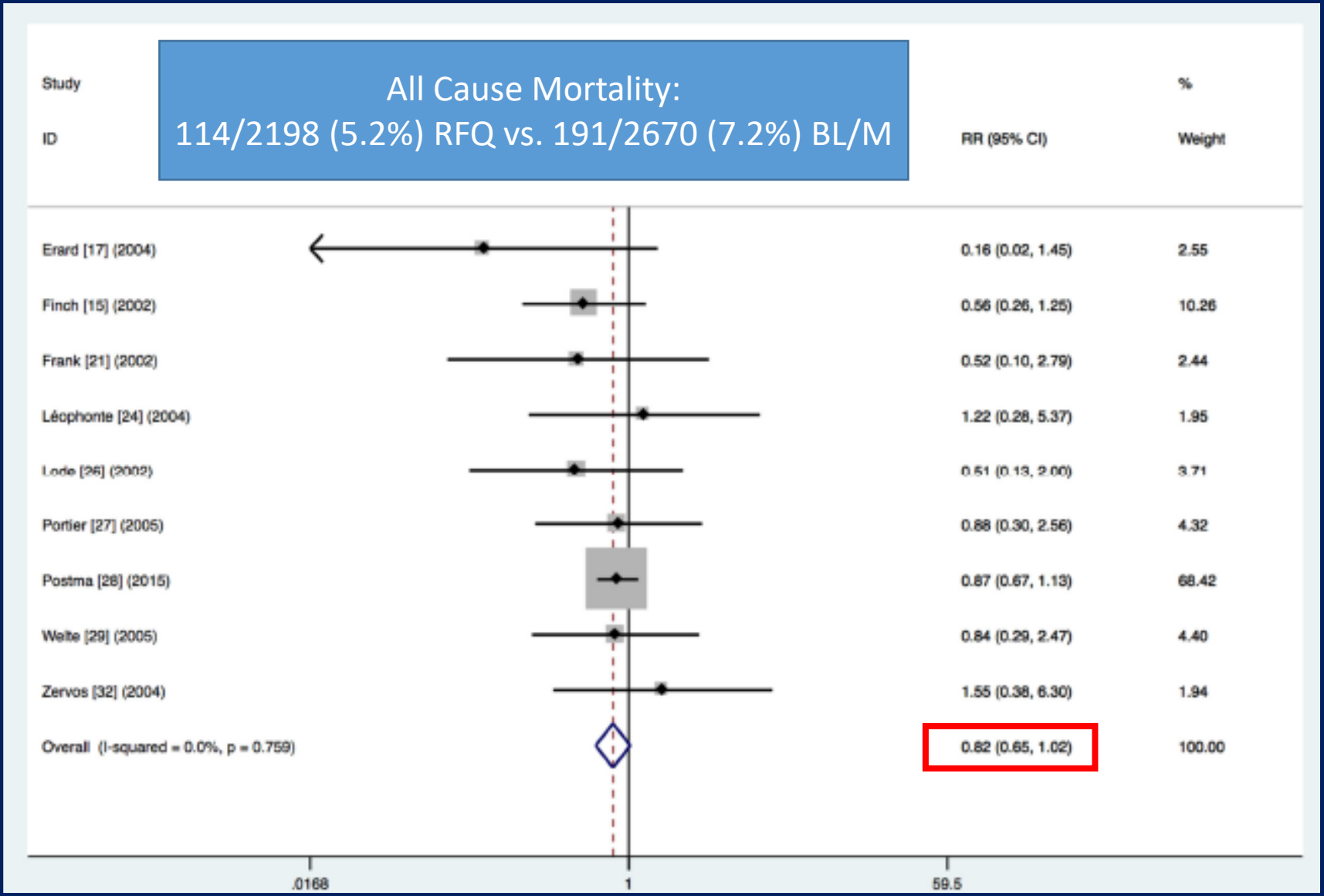
Clinical Question:
Is There a Preference in Empiric Antimicrobial Therapy for Patients Admitted to the Medical Floor with Non-Severe Disease?

FQ vs. Beta-lactam/Macrolide Therapy

- Meta-analysis combining RCTs evaluating a RFQ vs beta-lactam with or without a macrolide for the treatment of hospitalized, non-ICU patients with CAP up to 11/2018
- Primary outcome was all cause mortality
  - Secondary outcomes: clinical treatment success, length of stay, adverse events related to study treatment
- Twenty-two total studies were included in the final analysis involving 6,235 patients

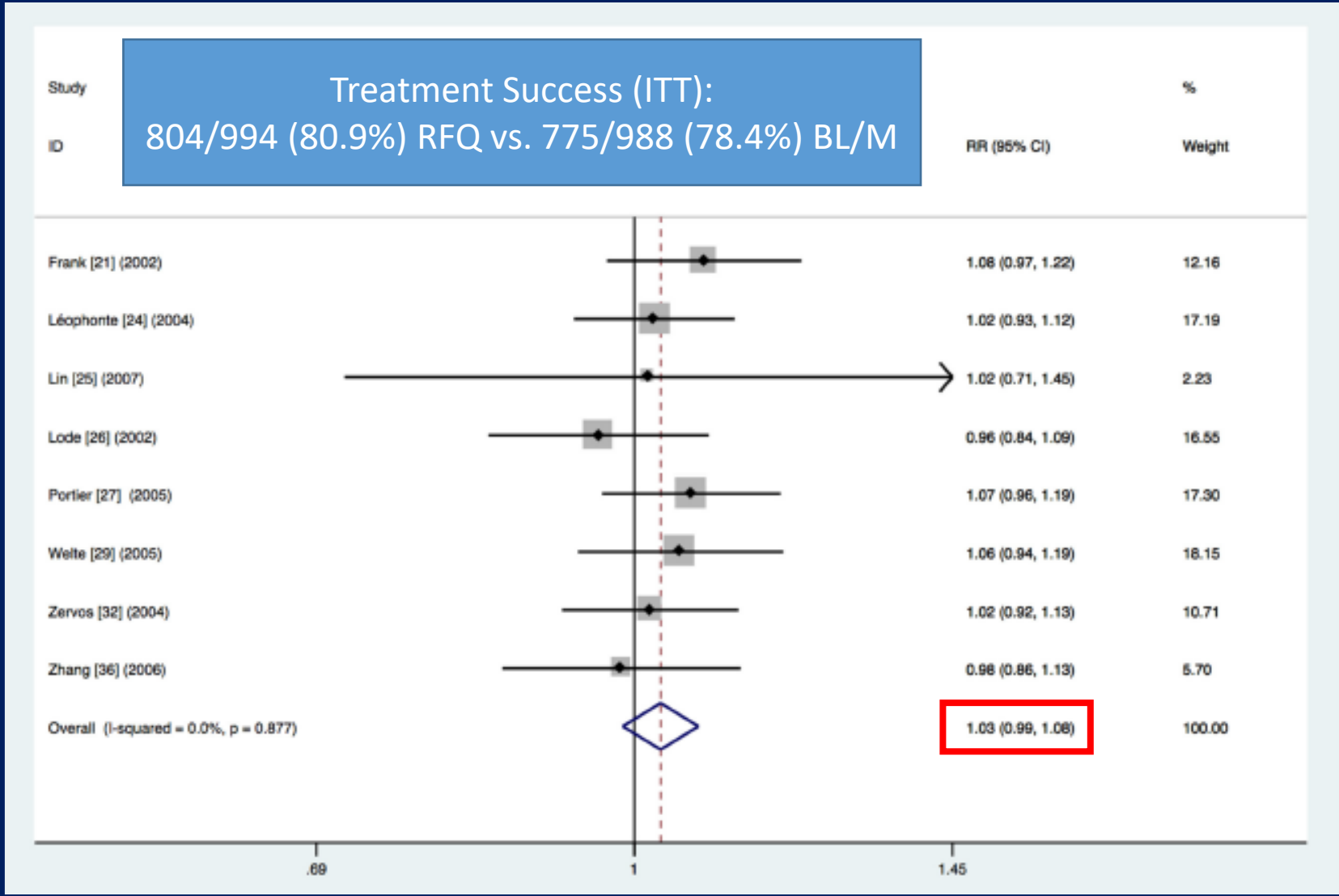
Li et al. *Front Pharmacol* 2019; 10: 1-13

Mortality Outcome



Li et al. *Front Pharmacol* 2019; 10: 1-13

Clinical Treatment Success Outcome



Li et al. *Front Pharmacol* 2019; 10: 1-13

Length of Stay and AEs

- LOS – no significant difference found in the 9 trials which reported LOS
- Adverse Events
  - 20/22 trials reported on AEs
  - Most were mild-moderate involving the GI tract or LFT abnormalities
  - QTc prolongation was only reported in 1 trial with one patient on amox/clav + clarithromycin
  - Overall: RR 0.87 (95% CI 0.77-0.97) – favoring RFQs
  - Withdrawal 2/2 AEs: 0.87 (95% CI 0.59-1.30)
    - Difference driven by GI AEs: 0.63 (95% CI 0.43-0.94)

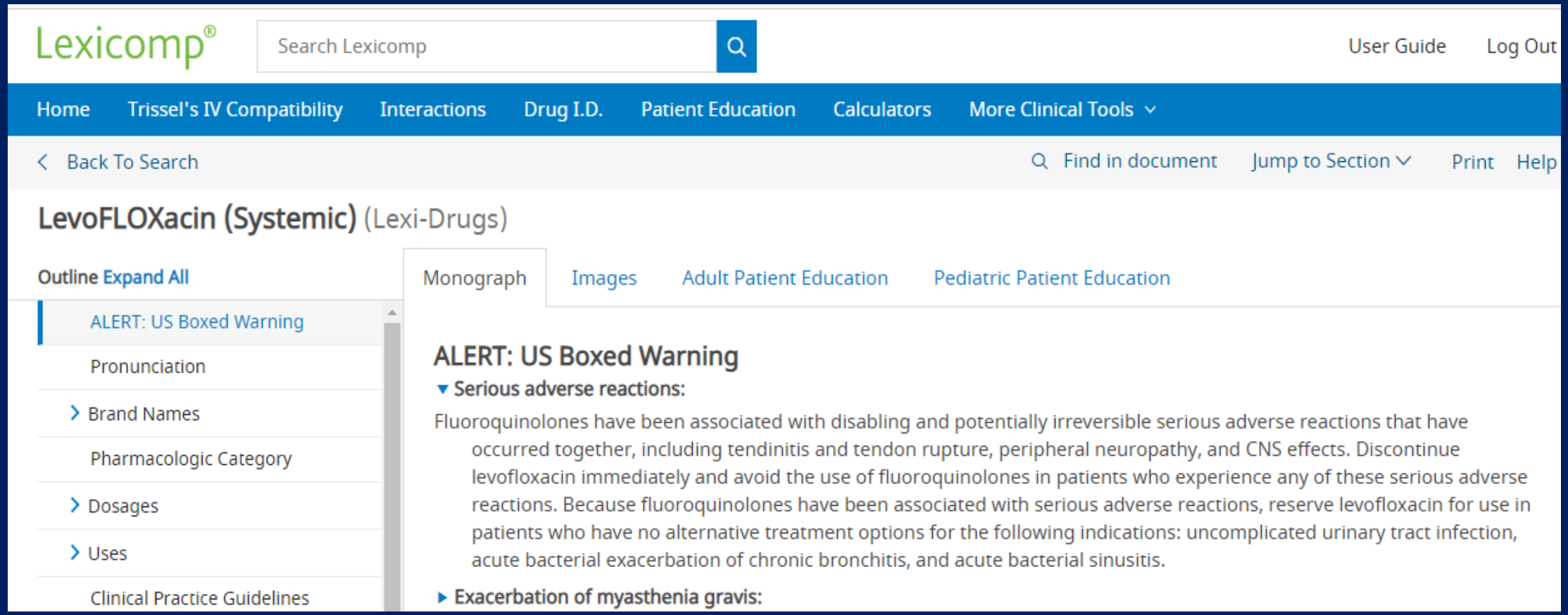
Li et al. *Front Pharmacol* 2019; 10: 1-13

Author's Conclusions

- "…fluoroquinolone monotherapy has similar efficacy and favorable safety compared with beta-lactams with or without a macrolide for non-ICU hospitalized CAP patients."

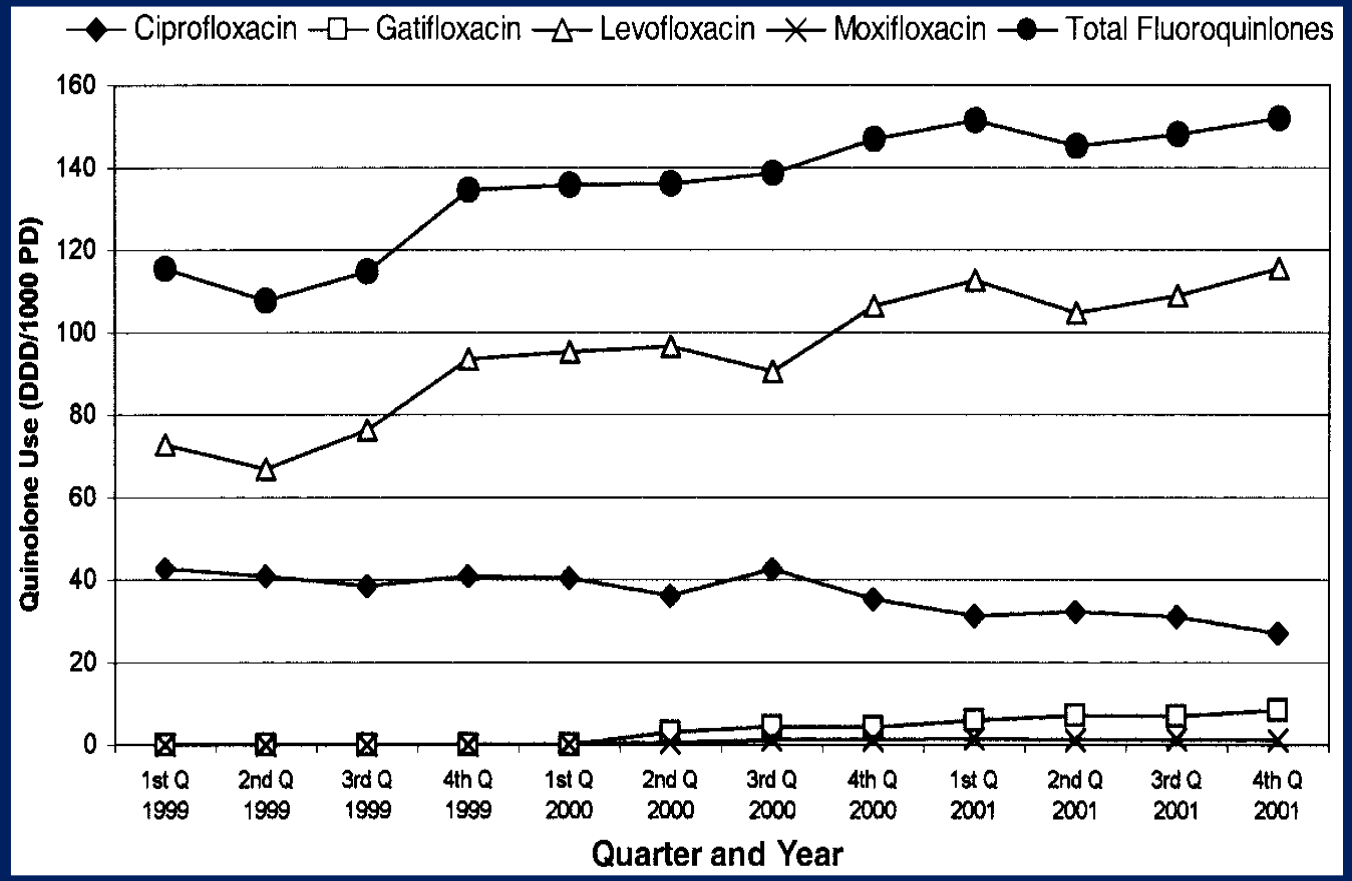
Li et al. *Front Pharmacol* 2019; 10: 1-13

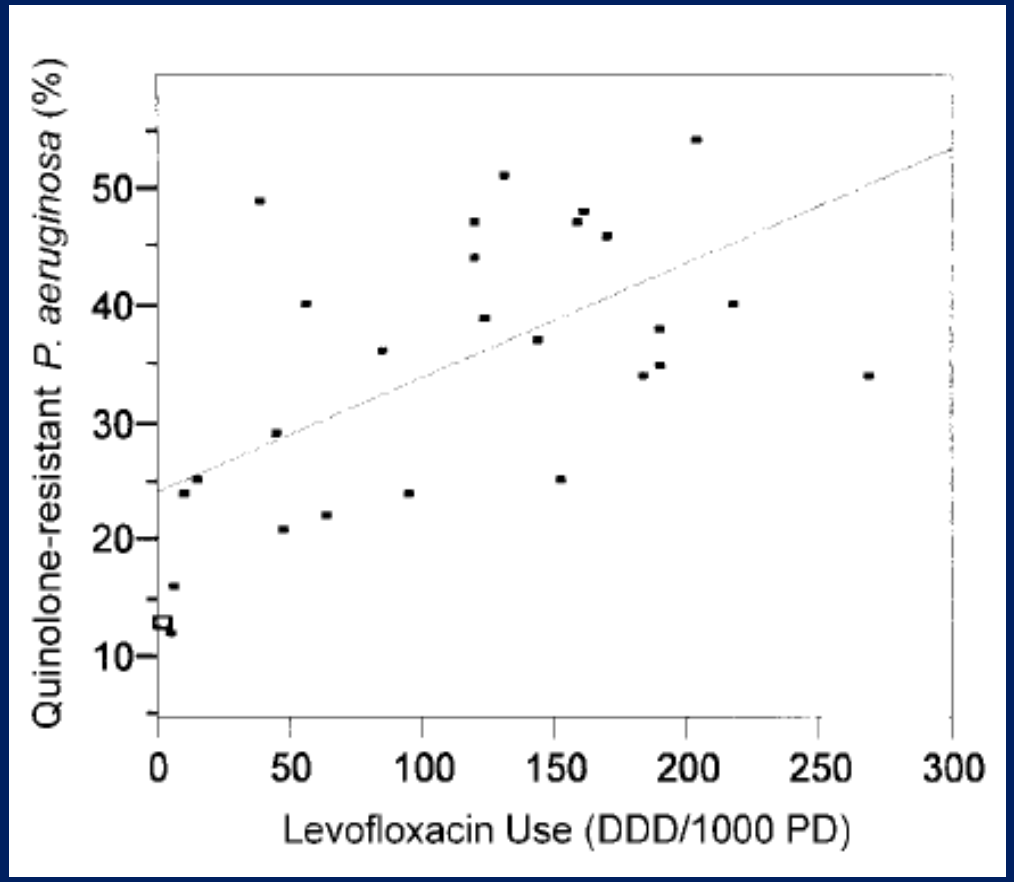
Why *May* We Think About Avoiding FQs?



FQ Use and Impact on Resistance

- Surveillance data from ~40 hospitals (and surrounding communities for outpatient FQs prescriptions) in the US from 1999-2001

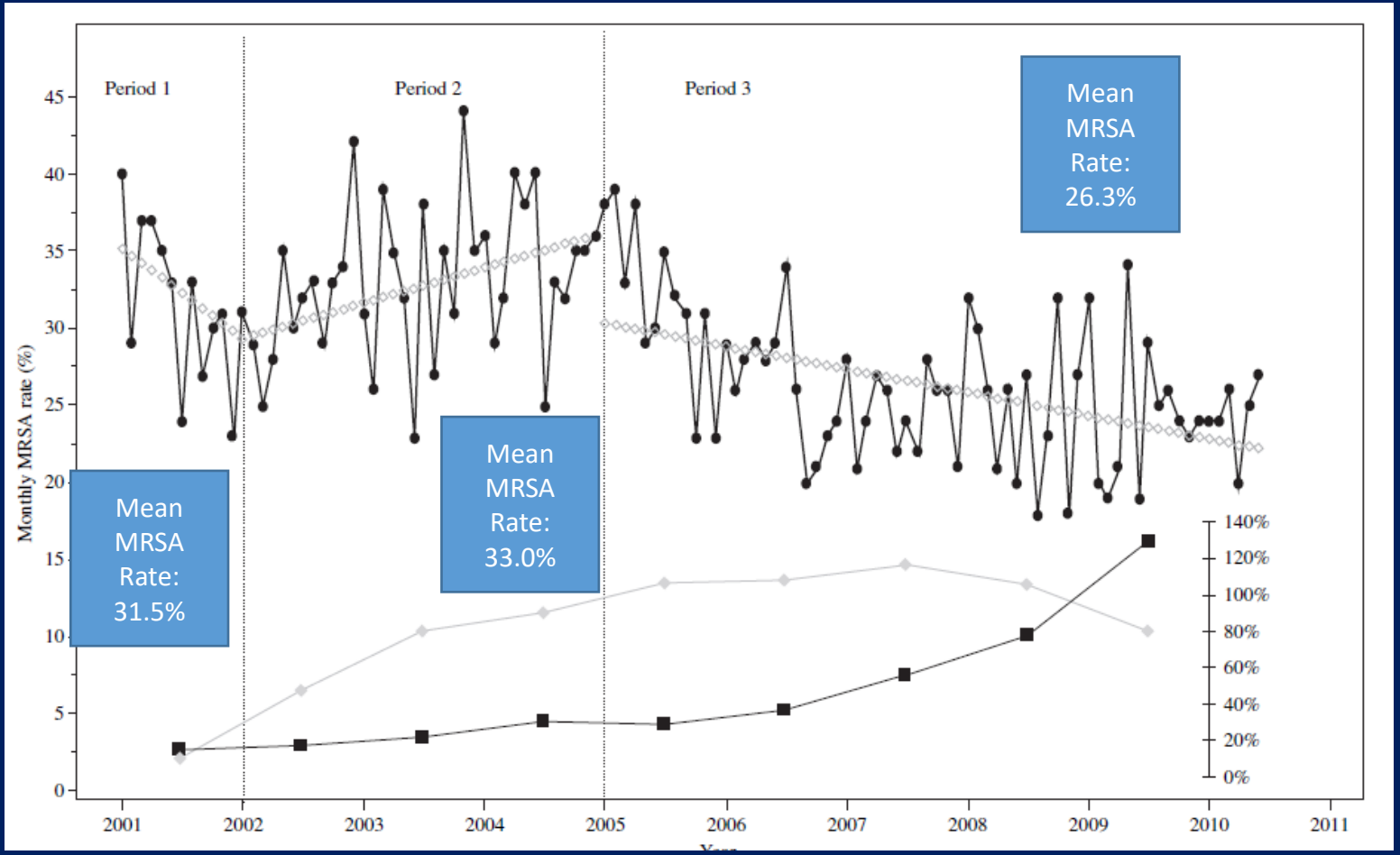




Polk et al. *Clin Infect Dis* 2004; 39: 497-503

Impact of FQ Use on MRSA Rates

- 10 years of data from a tertiary hospital in France
- 3 periods of study – FQ restriction, FQ release, hand hygiene campaign implementation



Parienti et al. *J Hosp Infect* 2011; 78: 118-22.

Cardiac Toxicity and CAP Therapy

- Post-hoc analysis of the CAP-START trial

Macrolide	aHR	FQ	aHR
New or Worsening Cardiac Event		**New or Worsening Cardiac Event**	
Azithromycin	0.76 (0.42-1.35)	*Ciprofloxacin*	0.70 (0.39-1.26)
Clarithromycin	1.03 (0.62-1.70)	*Levofloxacin*	0.43 (0.20-0.93)
Erythromycin	1.82 (1.23-2.68)	*Moxifloxacin*	0.56 (0.36-0.88)
New or Worsening Heart Failure		**New or Worsening Heart Failure**	
Azithromycin	0.78 (0.40-1.52	*Ciprofloxacin*	0.65 (0.32-1.31)
Clarithromycin	1.17 (0.66-2.08)	*Levofloxacin*	0.27 (0.08-0.86)
Erythromycin	2.11 (1.36-3.26)	*Moxifloxacin*	0.50 (0.27-0.87)
New or Worsening Arrythmia		**New or Worsening Arrythmia**	
Azithromycin	1.03 (0.43-2.47)	*Ciprofloxacin*	0.75 (0.29-1.93)
Clarithromycin	0.87 (0.36-2.12)	*Levofloxacin*	0.49 (0.15-1.62)
Erythromycin	1.28 (0.64-2.57)	*Moxifloxacin*	0.66 (0.33-1.34)

Postma et al. *BMC Infect Dis* 2019; 19: 1-12

Clinical Question:
Is There a Preference in Empiric Antimicrobial Therapy for Patients Admitted to the Medical Floor with Non-Severe Disease?

Data suggests equal efficacy amongst the options and, generally, tolerability is the same; however, >use of FQs = >resistance and *could* be contributing to CA and HA rates of MRSA.

Consideration for Practice: Use a beta-lactam + macrolide before a FQ

Clinical Question:
Is a Longer Course of CAP Therapy Associated with Better Outcomes?

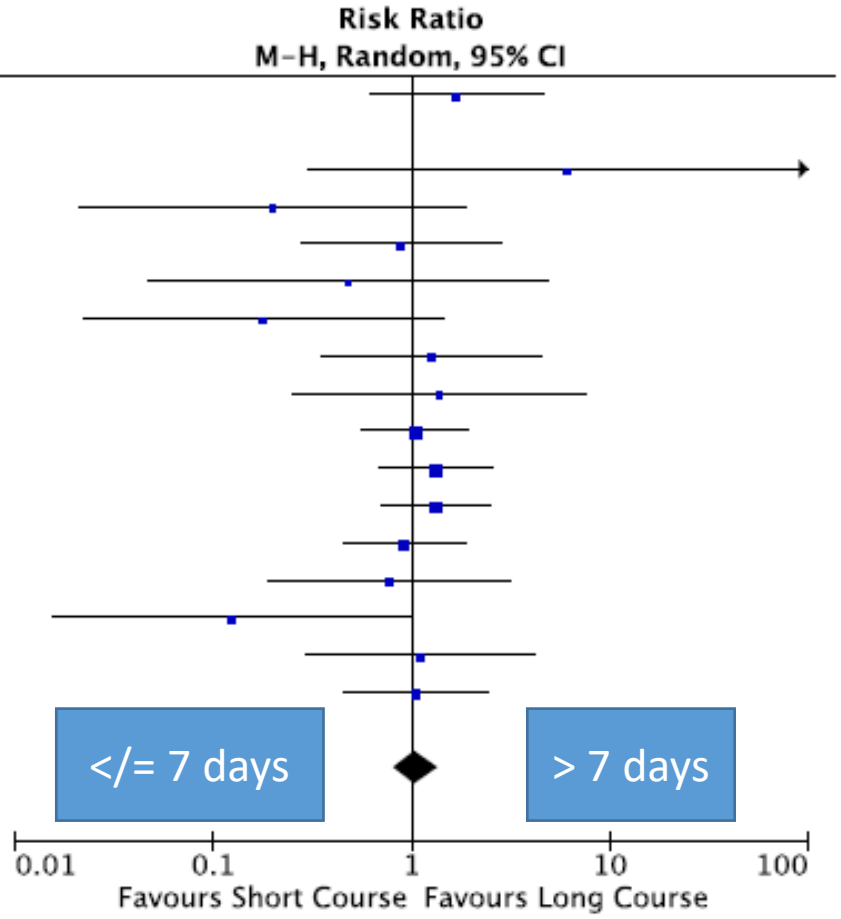
Systematic Review and Meta-Analysis of Short vs. Long-Course CAP Therapy

Non-duplicated RCTs:
Clinical Failure

Study or Subgroup	Short Term Events	Short Term Total	Long Term Events	Long Term Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Brion	9	46	5	43	6.3%	1.68 [0.61, 4.62]	1990
Schonwald A	0	39	0	32		Not estimable	1990
Kinasewitz	2	32	0	39	0.7%	6.06 [0.30, 121.87]	1991
Schonwald B	1	89	3	53	1.3%	0.20 [0.02, 1.86]	1994
Bohte	4	19	5	21	4.8%	0.88 [0.28, 2.82]	1995
Rizzato	1	20	2	19	1.2%	0.47 [0.05, 4.82]	1995
Kobayashi	1	59	6	63	1.5%	0.18 [0.02, 1.43]	1995
O'Doerthy	5	88	4	88	3.9%	1.25 [0.35, 4.50]	1998
Siegel	3	24	2	22	2.2%	1.38 [0.25, 7.47]	1999
Leophonte A	17	94	16	92	16.7%	1.04 [0.56, 1.93]	2002
Dunbar	15	128	17	192	14.8%	1.32 [0.69, 2.55]	2003
Tellier	35	320	12	146	16.4%	1.33 [0.71, 2.49]	2004
Leophonte B	13	115	14	113	12.8%	0.91 [0.45, 1.85]	2004
Sopena	3	31	4	32	3.2%	0.77 [0.19, 3.18]	2004
Rahav	1	62	6	46	1.5%	0.12 [0.02, 0.99]	2004
El Moussaoui	4	54	4	60	3.6%	1.11 [0.29, 4.23]	2006
File	11	247	10	236	9.1%	1.05 [0.45, 2.43]	2007
Total (95% CI)		**1467**		**1297**	**100.0%**	**1.05 [0.82, 1.36]**	
Total events	125		110				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 13.27$, df = 15 (P = 0.58); $I^2 = 0\%$

Test for overall effect: Z = 0.41 (P = 0.68)



Furlan et al. *Int Emerg Med* 2019; 14: 377-94.s

Clinical Question:
Is a Longer Course of CAP Therapy Associated with Better Outcomes?

No benefit has been observed for durations of treatment >7 days for CAP. Current IDSA guidelines state to treat for no less than 5 days.

Consideration for Practice: Duration of 5-7 days is optimal; 10-14 days offers no proven benefit

Audience Response Question

- Which of the following is the optimal treatment and duration for a patient admitted with non-severe community-acquired pneumonia?
  A. Ciprofloxacin 750mg PO BID x 5 days
  B. Moxifloxacin 400mg PO daily x 10 days
  C. Cefuroxime 500mg PO BID + doxycycline 100mg PO BID x 5 days
  D. Cefpodoxime 200mg PO BID + doxycycline 100mg PO BID x 10 days

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Pneumonia: HAP/VAP – 2016 Guidelines

Empiric Antibiotic Recommendations for HAP		
Not at high-risk for mortality and no factors increasing the likelihood of MRSA	**Not at high-risk for mortality BUT with factors increasing the likelihood of MRSA**	**High-risk of mortality or receipt of IV antibiotics during the prior 90 days**
Piperacillin/tazobactam OR *Cefepime OR* *Levofloxacin OR* *Imipenem/cilastatin OR* *Meropenem*	*Piperacillin/tazobactam OR* *Cefepime OR* *Levofloxacin OR* *Ciprofloxacin OR* *Imipenem/cilastatin OR* *Meropenem OR* *Aztreonam* **---PLUS---**	*Piperacillin/tazobactam OR* *Cefepime OR* *Imipenem/cilastatin OR* *Meropenem OR* *Aztreonam* **---PLUS---**
	Vancomycin OR *Linezolid*	*Levofloxacin OR* *Ciprofloxacin OR* *Amikacin OR* *Gentamicin OR* *Tobramycin* **---PLUS----**
	e61-111.	*Vancomycin OR* *Linezolid*

Kalil et al. *Clin Infect Dis* 2016; 63:

<u>High Risk for Mortality</u>

- Need for ventilatory support 2/2 pneumonia
- Septic shock

<u>Risk Factors Increasing the Likelihood of MRSA</u>

- IV antibiotics during the previous 90 days
- Treatment in a unit where the MRSA prevalence is not known OR >20%
- Presence of MRSA on culture or nasal screening

Pneumonia: HAP/VAP – 2016 Guidelines

Empiric Treatment Considerations for VAP		
All empiric regimens should include one of the following…	**MRSA coverage should be added if…**	**Two anti-pseudomonal agents (from different classes) if…**
Piperacillin/tazobactam OR *Cefepime OR* *Ceftazidime OR* *Imipenem/cilastatin OR* *Meropenem OR* *Aztreonam*	• Patient has received IV antibiotics in the last 90 days • The patient is in a unit where the MRSA incidence is >10-20% OR the incidence is not known *Vancomycin OR* *Linezolid*	• Patient has received IV antibiotics in the last 90 days • Septic shock at the time of VAP • ARDS preceding VAP • >/= 5 days of hospitalization prior to VAP • Acute renal replacement therapy prior to VAP onset • >10% of gram-negative isolates are resistant to an agent being considered for monotherapy *Ciprofloxacin* *Levofloxacin* *Amikacin OR* *Gentamicin OR* *Tobramycin OR* *Polymixin*

Kalil et al. *Clin Infect Dis* 2016; 63: e61-111.

Clinical Question:
Can We Use MRSA Nasal Surveillance as a Predictor of MRSA Pneumonia?

Meta-Analysis Evaluating the Utility of MRSA Nasal Screening in Predicting MRSA PNA

- Twenty-two studies involving 5163 patients were included through 11/2016

Type of Pneumonia	Studies, No.	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)	DOR (95% CI)	PPV, %	NPV, %
All	22	70.9 (58.8–80.6)	90.3 (86.1–93.3)	7.28 (5.3–10.1)	0.32 (0.22–0.46)	24.6 (13.6–37.5)	44.8	96.5
CAP/HCAP	4	85.0 (59.7–95.6)	92.1 (81.5–96.9)	10.8 (5.1–23.0)	0.16 (0.06–0.48)	66.4 (28.5–154.6)	56.8	98.1
VAP	5	40.3 (17.4–68.4)	93.7 (77.1–98.4)	6.34 (1.94–20.8)	0.63 (0.42–0.98)	9.96 (2.63–37.6)	35.7	94.8

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; DOR, diagnostic odds ratio; HCAP, healthcare-associated pneumonia; LR, likelihood ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; NPV, negative predictive value; PPV, positive predictive value; VAP, ventilator-associated pneumonia.

Parente et al. *Clin Infect Dis* 2018; 67: 1-7.

Clinical Question:
Can We Use MRSA Nasal Surveillance as a Predictor of MRSA Pneumonia?

Excellent negative predictive value, particularly for HCAP(!). Positive predictive value is not as helpful.

Consideration for Practice: Due to the high negative predictive value, certainly reasonable to use MRSA nasal screening as rationale to not initiate or stop vancomycin therapy.

Clinical Question:
Does it Matter if We Expose Fewer Patients to Vancomycin?

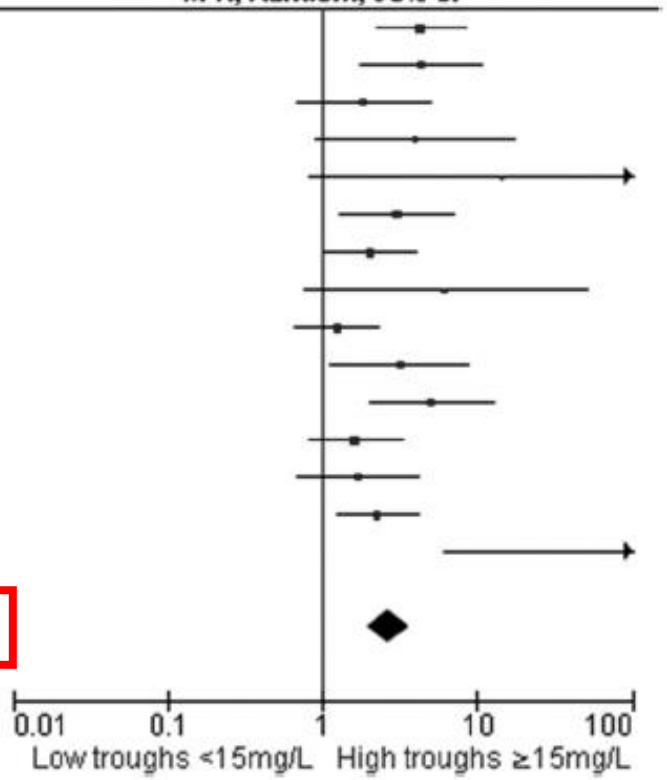
A Systematic Review & Meta-Analysis of Vancomycin-induced Nephrotoxicity

- Fifteen studies were included
- Incidence of nephrotoxicity varied from 5% to 43% between studies

Study or Subgroup	High troughs ≥15mg/L Events	Total	Low trough <15mg/L Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosso et al. (21)	42	142	13	146	9.8%	4.30 [2.19, 8.43]
Cano et al. (22)	22	89	7	99	7.2%	4.32 [1.74, 10.69]
Chung et al. (23)	12	25	16	48	6.5%	1.85 [0.69, 4.96]
Hermsen et al. (30)	5	16	4	39	3.6%	3.98 [0.91, 17.46]
Hidayat et al. (13)	11	63	0	32	1.1%	14.24 [0.81, 249.87]
Jeffres et al. (15)	27	49	13	45	7.7%	3.02 [1.28, 7.11]
Kralovicova et al. (31)	21	60	29	138	9.8%	2.02 [1.04, 3.96]
Kullar et al. (32)	8	116	1	84	2.0%	6.15 [0.75, 50.13]
Kullar et al. (8)	27	139	23	141	10.6%	1.24 [0.67, 2.28]
Lodise et al. (36)	7	27	14	139	6.2%	3.13 [1.12, 8.69]
McKamy et al. (38)	16	57	8	110	7.0%	4.98 [1.98, 12.52]
Minejima et al. (39)	17	72	25	155	9.6%	1.61 [0.80, 3.21]
Prabaker et al. (43)	7	54	24	294	7.3%	1.68 [0.68, 4.11]
Wunderink et al. (50)	26	118	24	215	10.7%	2.25 [1.22, 4.13]
Zimmermann et al. (51)	8	12	0	33	1.0%	126.56 [6.19, 2585.90]
Total (95% CI)		**1039**		**1718**	**100.0%**	**2.67 [1.95, 3.65]**
Total events	256		201			

Heterogeneity: Tau² = 0.14; Chi² = 23.89, df = 14 (P = 0.05); I² = 41%

Test for overall effect: Z = 6.13 (P < 0.00001)



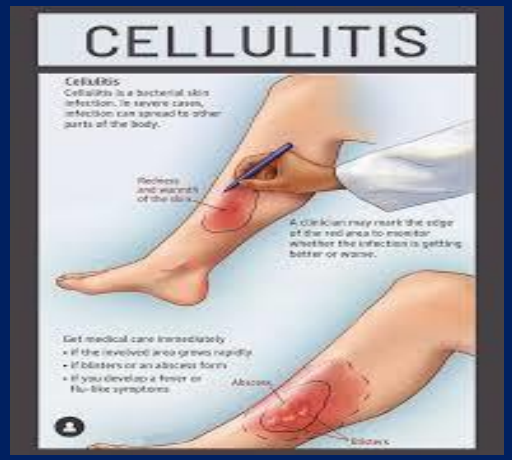
Van Hal et al. *Antimicrob Agents Chemother* 2013; 57: 734-44.

Clinical Question:
Does it Matter if We Expose Fewer Patients to Vancomycin?

If troughs of 15-20 are targeted (we'll get back to this later), the old goal trough for PNA, the risk of nephrotoxicity is increased significantly.

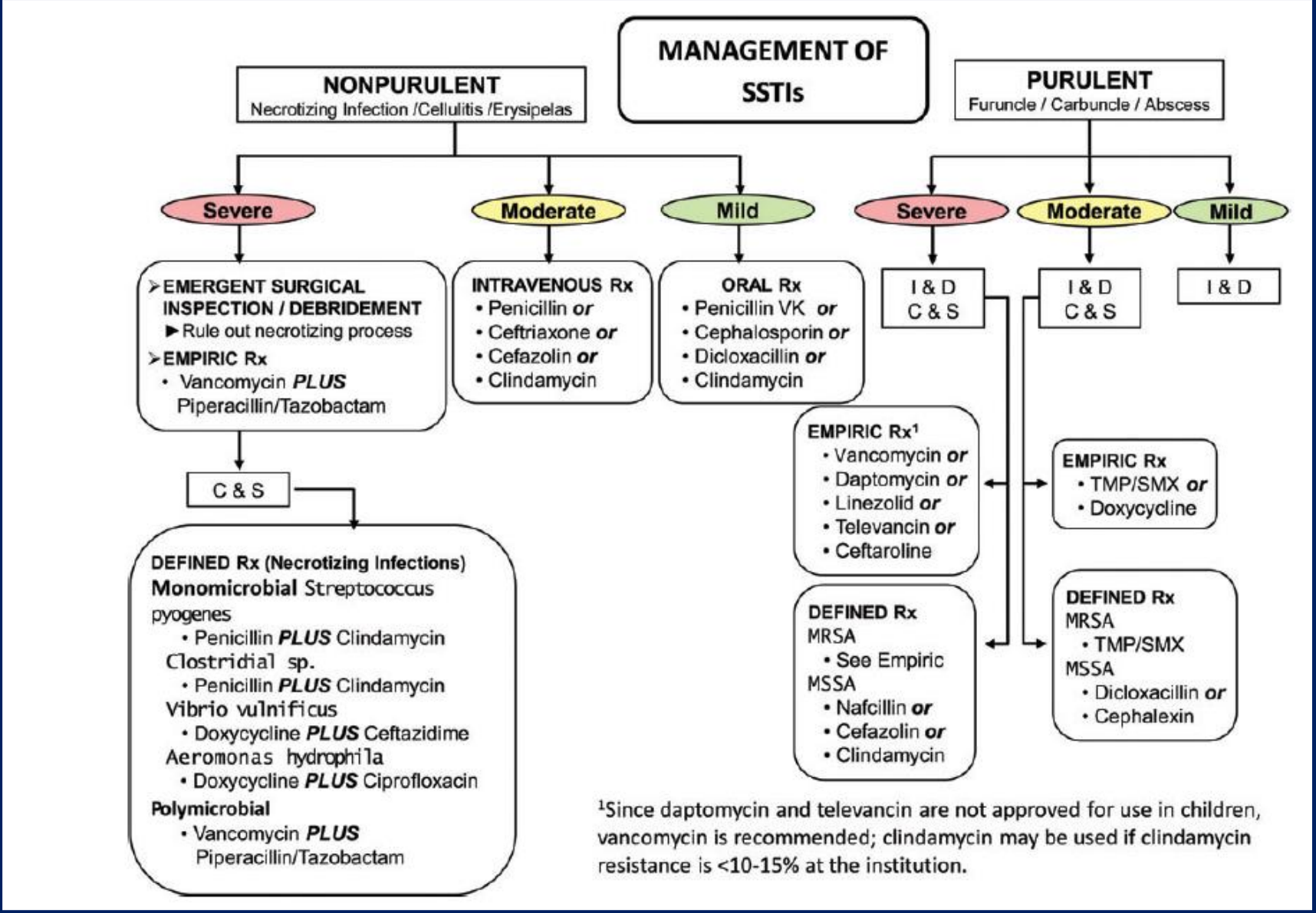
Consideration for Practice: Vancomycin-induced nephrotoxicity can/does happen and has been associated with routine doses used to obtain goal troughs for PNA. It is better NOT to use vancomycin if we don't have to.

Second Focus Area:



Cellulitis

2014 IDSA SSTI Guidelines



Recommended duration of treatment is 5 days.

Stevens et al. *Clin Infect Dis* 2014: 59: e10-52.

Clinical Question:
Are Outcomes Improved with Longer Durations of Treatment for SSTIs?

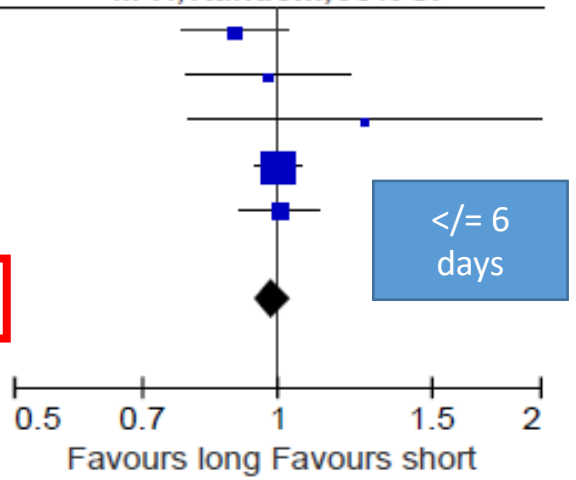
Meta-Analysis of the Treatment of Cellulitis and Erysipelas

- Forty-three studies were included including 5,999 evaluable patients
- Specifically for treatment duration, 5 studies evaluating 916 patients were included

	Short		Long			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Corey 2014	97	144	126	167	12.1%	0.89 [0.77, 1.03]	
Daniel 1991(1)	52	72	37	50	5.2%	0.98 [0.78, 1.21]	
Daniel 1991(2)	27	41	11	21	1.1%	1.26 [0.79, 2.00]	
Hepburn 2004	43	44	42	43	59.4%	1.00 [0.94, 1.07]	
Moran 2014	134	166	135	168	22.2%	1.00 [0.90, 1.12]	
Total (95% CI)		**467**		**449**	**100.0%**	**0.99 [0.94, 1.04]**	
Total events	353		351				

Heterogeneity: Tau² = 0.00; Chi² = 3.59, df = 4 (P = 0.46); I² = 0%

Test for overall effect: Z = 0.43 (P = 0.66)



eAnalysis 10.1. Primary outcome: Symptom free/reduced at the end of treatment comparing short versus long treatment courses.

Brindle et al. *JAMA Dermatol* 2019; 155: 1033-40.

Clinical Question:
Are Outcomes Improved with Longer Durations of Treatment for SSTIs?

Guidelines and available evidence suggest that for uncomplicated cellulitis (purulent or non-purulent) there is no advantage of longer durations of antimicrobial therapy

Consideration for Practice: In the outpatient setting, only treat patients with uncomplicated cellulitis with 5 days of antibiotics

Audience Response Question

- What is the guideline-recommeded empiric treatment and duration for a non-purulent SSTI in a patient without any allergies?
  A. Cephalexin 500mg PO four times a day x 5 days
  B. TMP/SMX 1 DS tab PO BID x 10 days
  C. Clindamycin 300mg PO four times a day x 5 days
  D. Amox/clav 875mg PO BID x 10 days

Audience Response Question

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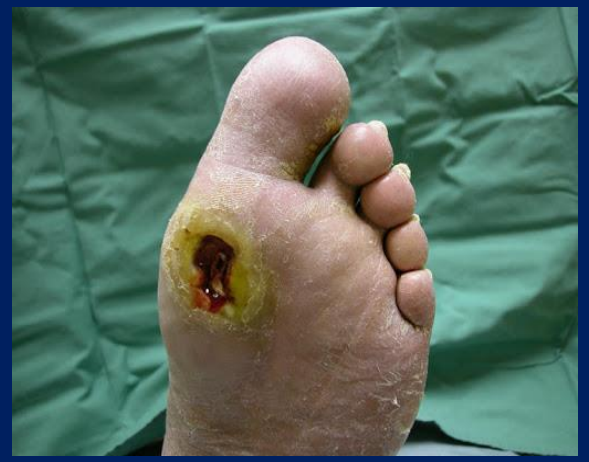
Third Focus Area:



Diabetic Foot Infections

2012 IDSA Diabetic Foot Infection Guidelines

Table 8. Suggested Empiric Antibiotic Regimens Based on Clinical Severity for Diabetic Foot Infections[a]

Infection Severity	Probable Pathogen(s)	Antibiotic Agent	Comments
Moderate (may be treated with oral or initial parenteral agent[s]) or severe (usually treated with parenteral agent[s])	MSSA; *Streptococcus* spp; Enterobacteriaceae; obligate anaerobes	Levofloxacin[b]	Once-daily dosing; suboptimal against *S. aureus*
		Cefoxitin[b]	Second-generation cephalosporin with anaerobic coverage
		Ceftriaxone	Once-daily dosing, third-generation cephalosporin
		Ampicillin-sulbactam[b]	Adequate if low suspicion of *P. aeruginosa*
		Moxifloxacin[b]	Once-daily oral dosing. Relatively broad-spectrum, including most obligate anaerobic organisms
		Ertapenem[b]	Once-daily dosing. Relatively broad-spectrum including anaerobes, but not active against *P. aeruginosa*
		Tigecycline[b]	Active against MRSA. Spectrum may be excessively broad. High rates of nausea and vomiting and increased mortality warning. Nonequivalent to ertapenem + vancomycin in 1 randomized clinical trial
		Levofloxacin[b] or ciprofloxacin[b] with clindamycin[b]	Limited evidence supporting clindamycin for severe *S. aureus* infections; PO & IV formulations for both drugs
		Imipenem-cilastatin[b]	Very broad-spectrum (but not against MRSA); use only when this is required. Consider when ESBL-producing pathogens suspected
	MRSA	*Linezolid*[b]	Expensive; increased risk of toxicities when used >2 wk
		Daptomycin[b]	Once-daily dosing. Requires serial monitoring of CPK
		Vancomycin[b]	Vancomycin MICs for MRSA are gradually increasing
	Pseudomonas aeruginosa	***Piperacillin-tazobactam***[b]	TID/QID dosing. Useful for broad-spectrum coverage. *P. aeruginosa* is an uncommon pathogen in diabetic foot infections except in special circumstances (2)

These guidelines are:

1. Getting old
2. Not as helpful, or specific, about empiric regimen selection

Lipsky et al. *Clin Infect Dis* 2012; 54: e132-73.

Two Relevant Clinical Questions

1. When do we need to use empiric coverage against MRSA?
2. When do we need to use empiric coverage against *Pseudomonas*?

Clinical Question:
When do we need to use empiric coverage against MRSA?

National VA Study Evaluating the Utility of MRSA Nasal Screening in Stewardship

- National VA data from 1 January 2007 to 1 January 2018
- Data from 121 different VAMCs were included
  - 245,833 unique patients were included
- This study went BEYOND just looking at nasal screening as a tool for PNA evaluation

Table 1. Efficacy Characteristics of Methicillin-Resistant *Staphylococcus aureus* Nares Screening by Culture Site

Type	Number	Male	Age, y	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Predictive Value, % (95% CI)	NPV, % (95% CI)	*P* Value	First Isolate Cohort Number[a]	NPV[a] (first isolate), % (95% CI)
Whole cohort	561 325	540 583 (96.3%)	68.2 ± 12.3	67.4 (67.0% to 67.9%)	81.2 (81.1% to 81.3%)	24.6 (24.4% to 24.8%)	96.5 (96.4% to 96.52%)	<.0001	418 031	95.7 (95.7% to 95.8%)

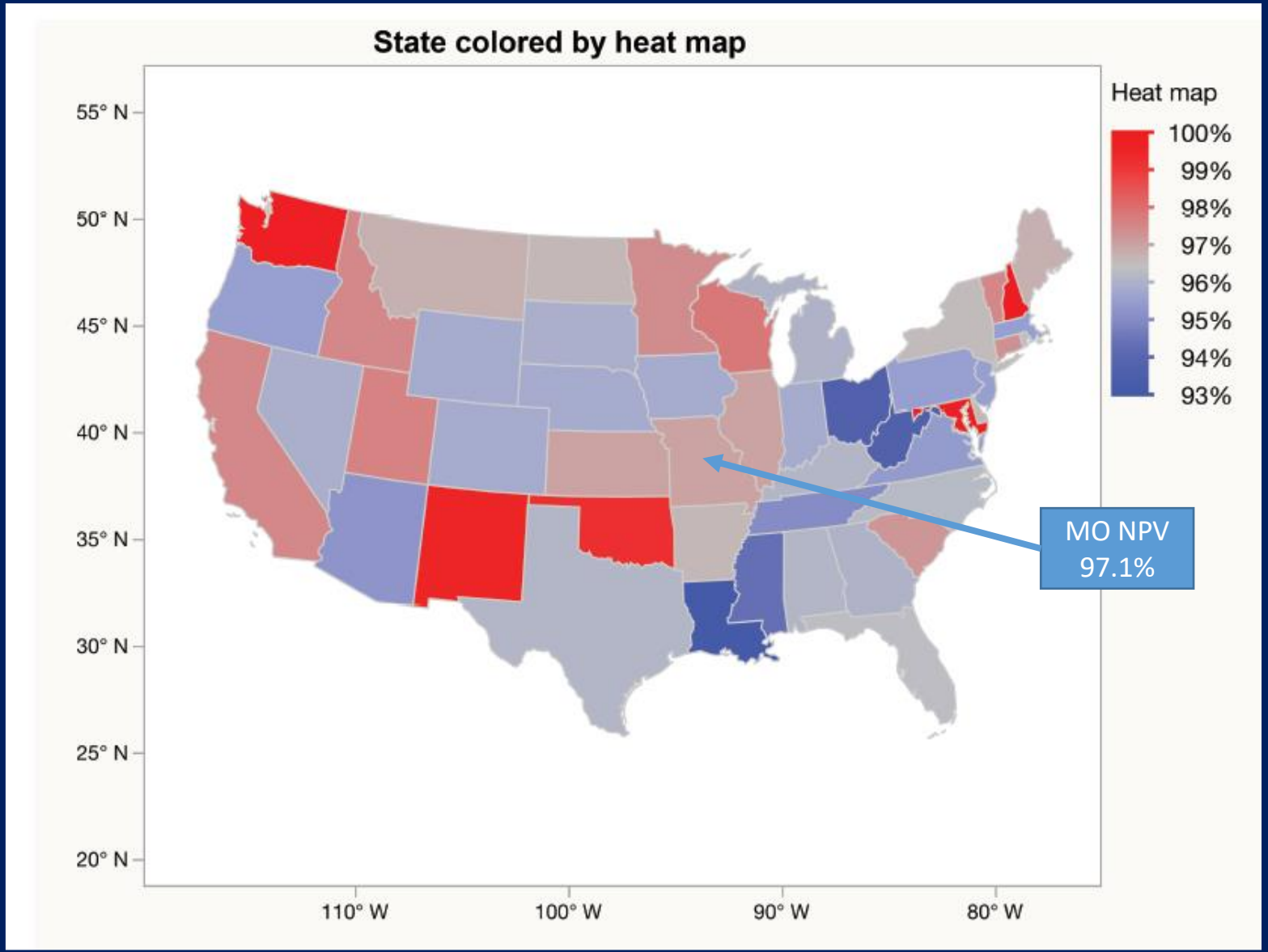
Mergenhagen et al. *Clin Infect Dis* 2020; 71: 1142-8.

National VA Study Evaluating the Utility of MRSA Nasal Screening in Stewardship

Type	Number	Male	Age, y	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Predictive Value, % (95% CI)	NPV, % (95% CI)	*P* Value
Wound	136 078	132 038 (97.0%)	65.1 ± 11.7	59.8 (59.1% to 60.5%	82.5 (82.3% to 82.7%)	34.2 (33.8% to 34.6%)	93.1 (93.0% to 93.3%)	<.0001
Wound sterile (UE, LE, foot)	18 956	18 615 (98.2%)	64.8 ± 10.5	53.1 (51.1% to 55.1%)	86.3 (85.8% to 86.9%)	36.6 (35.3% to 37.8%)	92.6 (92.3% to 92.8%)	<.0001
Wound sterile (all)	72 542	70 396 (97.0%)	64.7 ± 11.4	58.3 (57.3% to 59.3%)	85.4 (85.1% to 85.6%)	36.2 (35.6% to 36.8%)	93.5 (93.3% to 93.6%)	<.0001
Wound (LE, foot)	28 249	27 736 (98.2%)	65.4 ± 10.6	54.2 (52.5% to 55.9%)	84.9 (84.4% to 85.3%)	33.6 (32.6% to 34.5%)	92.9 (92.7% to 93.2%)	<.0001
Wound (UE)	2867	2782 (97.0%)	61.3 ± 13.0	62.9 (59.1% to 66.6%)	84.8 (83.2% to 86.3%)	55.7 (52.9% to 58.5%)	88.3 (87.2% to 89.3%)	<.0001
Wound (sacral)	2781	2680 (96.4%)	64.5 ± 12.8	58.7 (53.2% to 64.1%)	77.6 (75.9% to 79.3%)	26.2 (24.1% to 28.6%)	93.3 (92.4% to 94.1%)	<.0001

Mergenhagen et al. *Clin Infect Dis* 2020; 71: 1142-8.

Heat Map of NPVs by State



Mergenhagen et al. *Clin Infect Dis* 2020; 71: 1142-8.

Author's Conclusions

- "This study suggests that a negative MRSA nares swab taken within 7 days of culture is useful for predicting the absence of MRSA in a subsequent clinical culture."

Mergenhagen et al. *Clin Infect Dis* 2020; 71: 1142-8.

Clinical Question:
When do we need to use empiric coverage against MRSA?

Large-scale cohort studies DO suggest a high negative predictive value for MRSA nasal swabs and lower extremity wound infections (DFIs)

Consideration for Practice: For your next DFI patient with a negative MRSA swab ask yourself if you *really* need vancomycin

Clinical Question:
When do we need to use empiric coverage against *Pseudomonas*?

Understanding the Incidence of *Pseudomonas* in DFIs

- Cross-sectional study of patients presenting with a DFI to an urban county hospital in Denver, CO between 1 June 2012 and 31 December 2013
- One hundred and twelve patients were included

Pseudomonas isolation was not associated with any measured risk factor (E.g. age, previous abx use in the last 90 days, infection severity, etc.)

Table 1. Bacteria Isolated from Bone and Tissue Cultures of 112 Patients with a Diabetic Foot Infection

Bacteria	Patients (No. [%])
Streptococcus	54 (48.2)
Staphylococcus aureus	48 (42.9)
Coagulase-negative staphylococcus	48 (42.9)
Enterococcus	16 (14.3)
Enterobacteriaceae	24 (21.4)
Pseudomonas aeruginosa	5 (4.5)
Anaerobic bacteria	41 (36.6)

Young et al. *J Am Podiatr Med Assoc* 2015; 105: 125-9.

Potential Risk Factors for *Pseudomonas* in DFIs

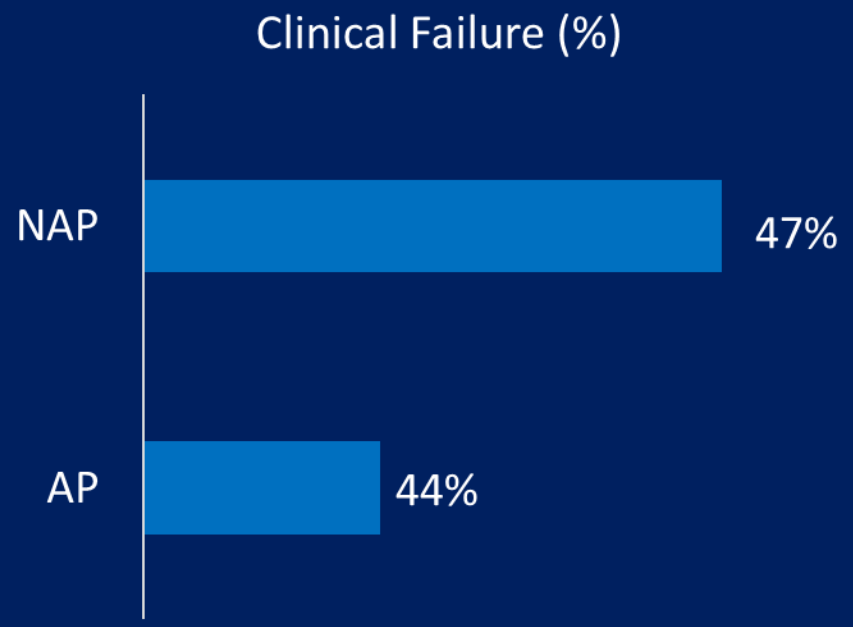
- Microbiologic sub-analysis of a study in Turkey in patients with diabetic foot wounds from 1 January 2012 to 31 December 2013
- Ninety patients with cultures included in this analysis

Total % of Pseudomonal Isolates: 25.8% (23/89)		
Variable	OR (95% CI)	*P*-value
Previous lower extremity amputation	12.86 (3.85-42.44)	<0.001
Previous active wound dressing	5.99 (1.36-26.33)	0.018

Ertugrul et al. *J Am Podiatr Med Assoc* 2017; 107: 483-9.

Empiric Anti-Pseudomonal Therapy vs. No Empiric Pseudomonal Coverage

- Retrospective cohort analysis of patients at the VA St. Louis treated for *Pseudomonas*-negative OM between 1 January 2009 and 31 July 2015



	Clinical Cure (n=54)	Clinical Failure (n=55)	P-value
Antipseudomonal Therapy	19	24	0.37
History of OM	12	8	0.30
DM	46	49	0.54
PVD	20	18	0.64
MRSA Therapy	33	35	0.77
Surgical Intervention	30	21	0.07

Jansen et al. *Open Forum Infect Dis* 2017; 4 (Suppl 1): S97.

Clinical Question:
When do we need to use empiric coverage against *Pseudomonas*?

The incidence of *Pseudomonas* in diabetic foot infections appears to be low based on epidemiologic data. Clear risk factors for pseudomonal infection are difficult to find, but could include a wet or macerated wound, previous lower extremity amputation, and previous active wound dressing.

Consideration for Practice: Consider potential risk factors before starting all DFI patients on empiric therapy active against *Pseudomonas*.

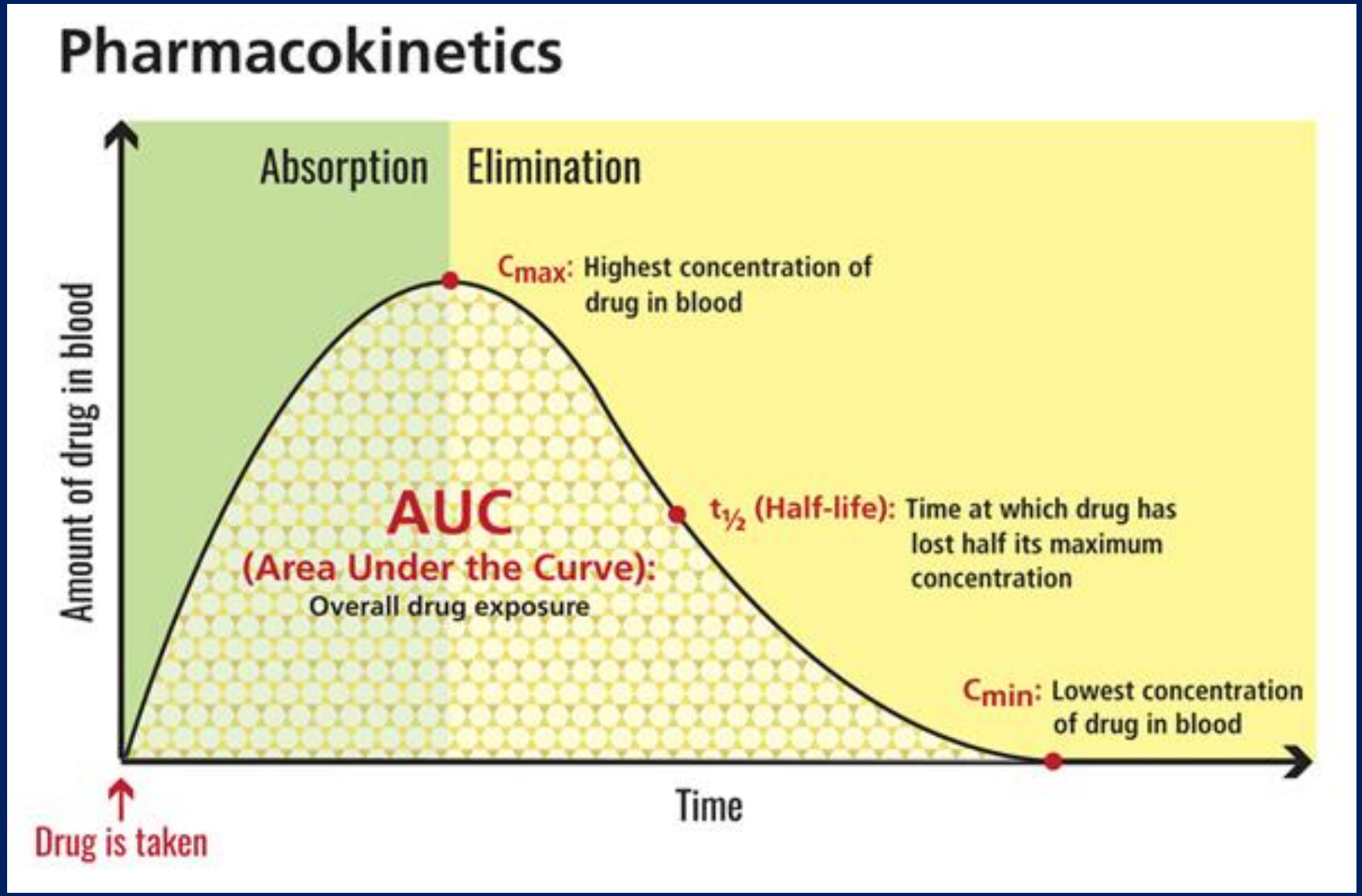
Focus Area: Antimicrobial Dosing

New Vancomycin Dosing Guidelines - 3/2020

- Preponderance of evidence reinforcing that AUC is the PK/PD parameter most associated with vancomycin efficacy
- The 2009 guidelines acknowledged that, but felt that, for most infections, a trough surrogate of 15-20 mcg/mL would achieve that AUC/MIC and minimize toxicity (e.g. AKI)
- Evidence reported since the guideline publication has indicated that the AUC/MIC goal can be achieved with *lower* troughs AND this could minimize the risk of AKI
- The new guidelines have done away with trough goals and advocate for an AUC between 400-600

Rybak et al. *Am J Health Syst Pharm* 2020; 77: 835-63.

What is Area-Under-the-Curve (AUC)?



Clinical Question:
What are the benefits of AUC-based vancomycin dosing compared to trough-based dosing?

AUC-based Dosing vs. Trough-based Dosing in Patients with MRSA Bacteremia

- Retrospective cohort of patients in the Allegheny Health Network from 1 January 2016 – 31 August 2018
- One hundred nineteen patients were included
- Outcomes were **vancomycin TDD** and AKI

BMI Group	Vancomycin TDD, Mean (SD), Trough-Based Dosing	Vancomycin TDD, Mean (SD), AUC-Based Dosing	*P* Value
≥30 kg/m^2 (n = 68)	2637.25 (1327.89)	1918.71 (625.89)	<0.0001
<30 kg/m^2 (n = 51)	2205.88 (1115.48)	2034.84 (608.68)	0.3388
Total (n = 119)	2390.76 (1224.59)	1985.07 (616.18)	0.0014

Abbreviations: AUC, area under the curve; BMI, body mass index; MIC, minimum inhibitory concentration; TDD, total daily dose.

AKI:
Total Cohort: 38.7% (46/119)
High BMI vs. Low BMI: 54.9% vs. 26.5% (*P*=0.002)

Covvey et al. *Ann Pharmacother* 2020; 54: 644-51.

Author's Conclusions

- "An AUC-based dosing strategy utilizes a lower TDD, which may lead to lower rates of AKI compared to traditional trough-based dosing strategies."

Covvey et al. *Ann Pharmacother* 2020; 54: 644-51.

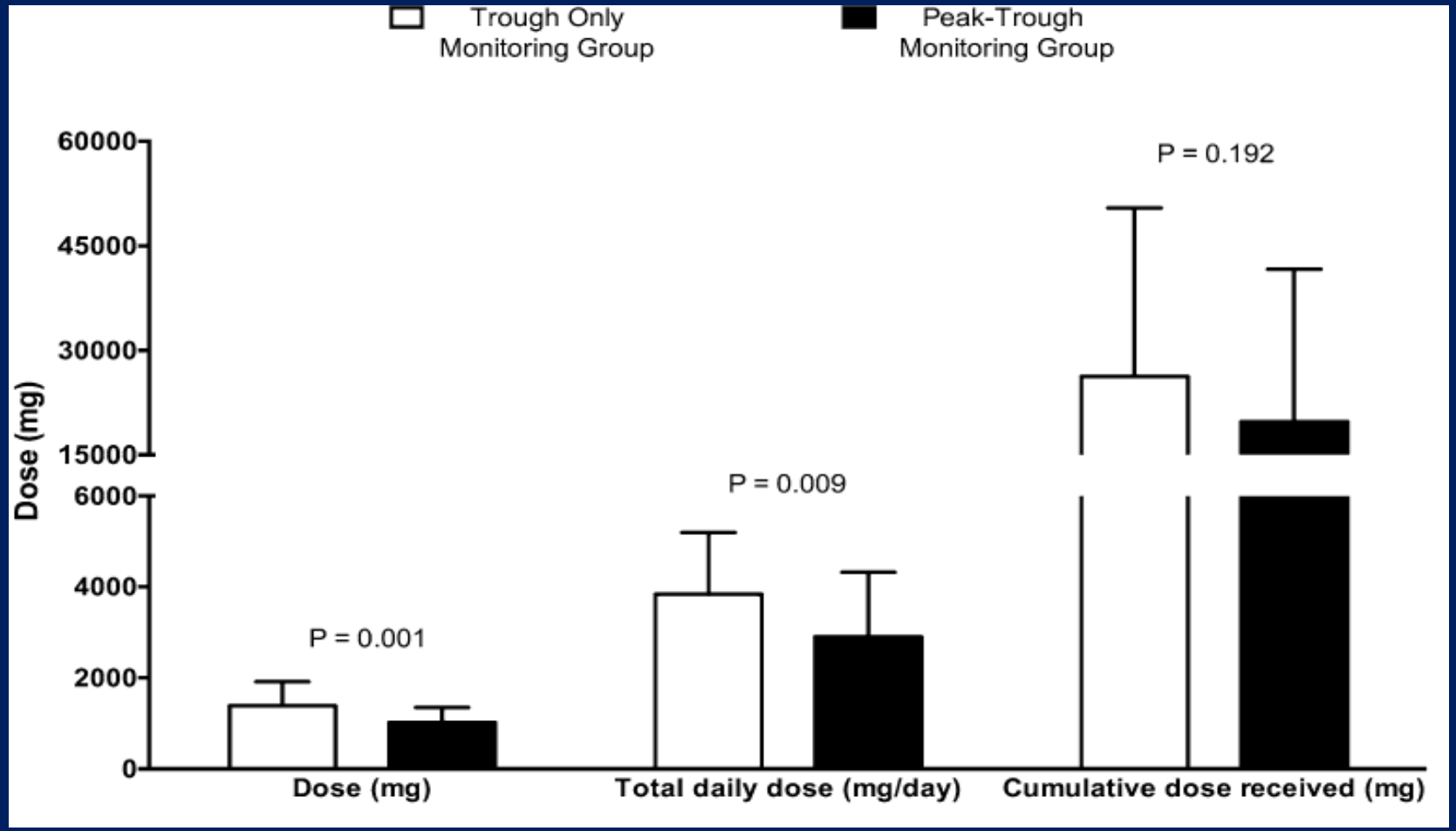
Clinical Outcomes of Trough-based Monitoring vs. Peak-trough-based Monitoring

- Multicenter, parallel group RCT at 3 hospitals in Qatar
- A variety of infections in which vancomycin was used for at least 3 days

Variable	Trough-only-monitoring group ($n=35$)	Peak–trough-monitoring group ($n=30$)	p value[a]
Vancomycin treatment efficacy outcomes, n (%)			
Therapeutic cure	17 (48.6)	23 (76.7)	0.020
Therapeutic failure	18 (51.4)	7 (23.3)	
Vancomycin treatment safety outcomes, n (%)			
Neutropenia	3 (8.6)	1 (3.3)	0.381
Nephrotoxicity	1 (2.9)	1 (3.3)	0.912

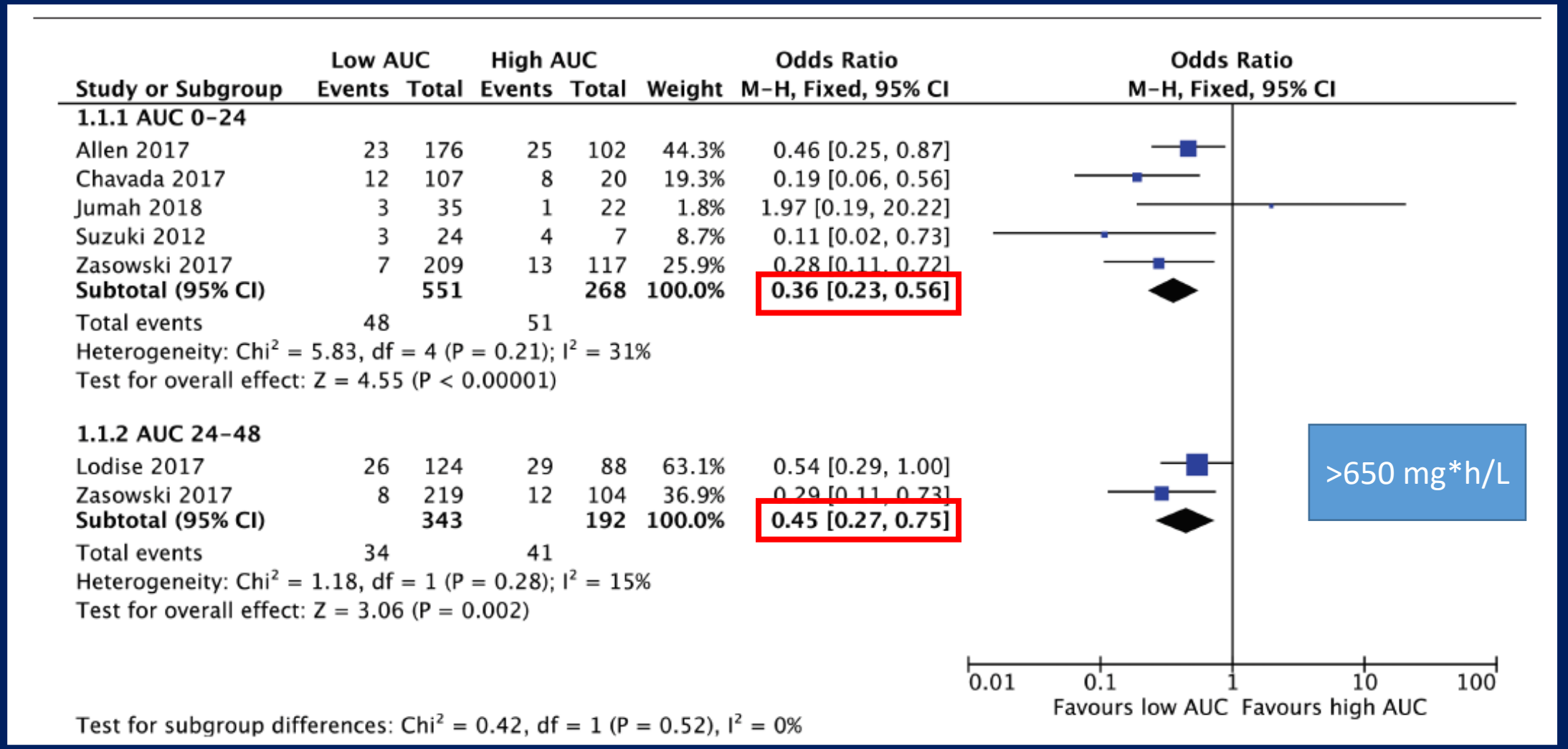
Al-Sulati et al. *Eur J Drug Metabol Pharmacokin* 2019; 44: 639-52.

Clinical Outcomes of Trough-based Monitoring vs. Peak-trough-based Monitoring



Al-Sulati et al. *Eur J Drug Metabol Pharmacokin* 2019; 44: 639-52.

Meta-Analysis of Vancomycin AUC and AKI



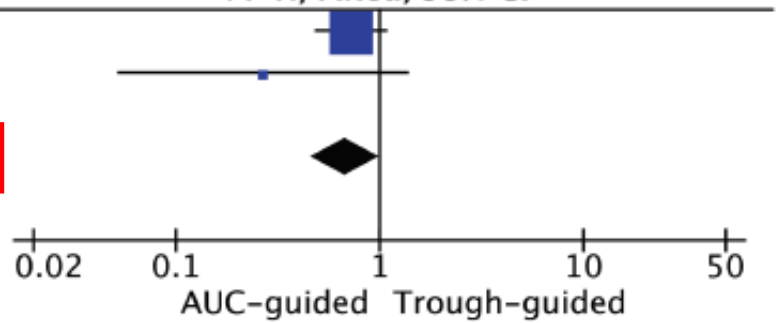
Aljefri et al. *Clin Infect Dis* 2019; 69: 1881-7.

Meta-Analysis of Vancomycin AUC and AKI

Study or Subgroup	AUC guided Events	Total	Trough guided Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Finch 2017	54	734	54	546	90.1%	0.72 [0.49, 1.07]
Neely 2017	2	88	6	75	9.9%	0.27 [0.05, 1.37]
Total (95% CI)		**822**		**621**	**100.0%**	**0.68 [0.46, 0.99]**
Total events	56		60			

Heterogeneity: $Chi^2 = 1.35$, $df = 1$ ($P = 0.24$); $I^2 = 26\%$

Test for overall effect: $Z = 2.00$ ($P = 0.05$)



Aljefri et al. *Clin Infect Dis* 2019; 69: 1881-7.

Clinical Question:
What are the benefits of AUC-based vancomycin dosing compared to trough-based dosing?

Decreased vancomycin exposure, not sacrificing efficacy, likely decrease in rates of AKI.

Consideration for Practice: If you aren't certain if your health system has implemented AUC dosing speak with your pharmacy and ask about their plans for implementation.

Audience Response Question

- Which of the following is the guideline-recommended AUC range for vancomycin dosing?
  A. 1200-1500 mg*h/L
  B. 800-1200 mg*h/L
  C. 600-800 mg*h/L
  D. 400-600 mg*h/L

Audience Response Question

- Which of the following is the guideline-recommended AUC range for vancomycin dosing?
  A. 1200-1500 mg*h/L
  B. 800-1200 mg*h/L
  C. 600-800 mg*h/L
  D. 400-600 mg*h/L

Summary

- Pneumonias
  - CAP -> Consider using BL + macrolide over FQs and only treating for 5-7 days
  - HAP/VAP -> Consider using MRSA nasal swabs to de-escalate therapy
- SSTIs
  - For uncomplicated cellulitis only treat patients for 5 days
- DFIs
  - Not everyone requires empiric coverage for MRSA and *Pseudomonas*
  - Consider using MRSA nasal surveillance to avoid empiric vancomycin
  - *Pseudomonas* risk factors are hard to identify, but could include a macerated wound, previous lower extremity amputation, and previous active wound therapy
- Vancomycin Dosing
  - By utilizing the guideline-recommended AUC dosing we decrease vancomycin exposure, maintain efficacy, and potentially decrease rates of AKI

Final Thoughts

- Stewardship is everyone's responsibility
- It's about picking the right drug, at the right dose, for the right amount of time
- The implications of not paying attention to antimicrobial stewardship will affect everyone – the patient your prescribing for right now may not suffer the consequence, but your patient or a collogues patient a year from now could become infected with an organism for which there is no active antimicrobial therapy

Antimicrobial Stewardship for the Practicing Clinician

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