CSiM | CENTER FOR STEWARDSHIP IN MEDICINE

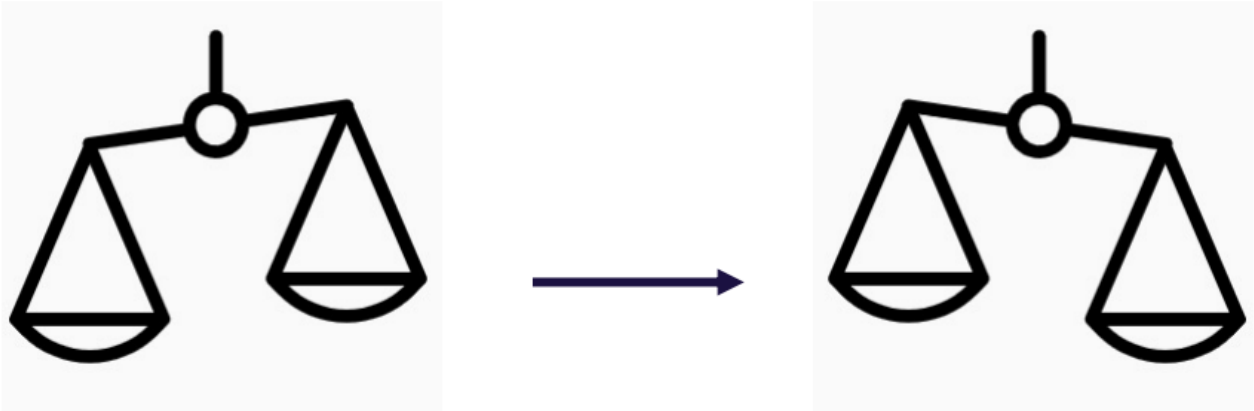
December 15, 2022

IQIC 101 Session 4

Agenda:

- Antibiotic harms – Whitney Hartlage, PharmD
- SMART goals discussion - All
- Wrap-up

Recap

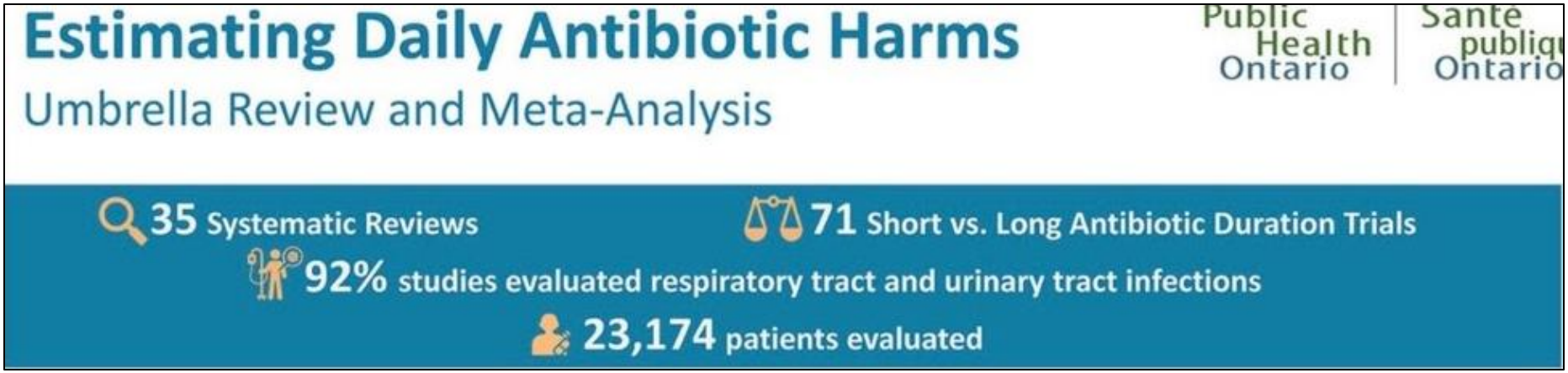


IDSA ASB Guidelines

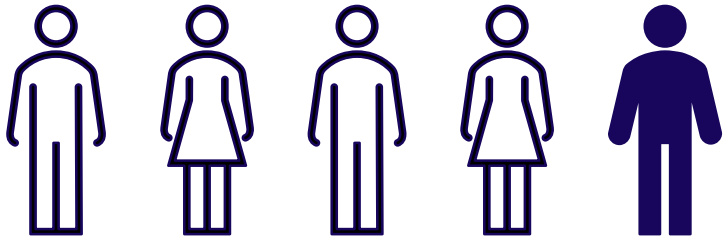
"We make a strong recommendation because there is high certainty for **harm** and low certainty of any benefit from treatment of ASB in older adults"

Nicolle et al. Clin Infect Dis. 2019.

Antibiotic Harms



4,565 Harm events = **19.6%**

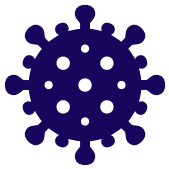


Curran et al. Clin Micro Infect. 2021.

Antibiotic Harms

1) Adverse drug events

2) Super infections



3) Antimicrobial resistance

4) Drug interactions

Adverse Drug Events (ADE) by Setting

Hospital, Community, Mixed

- 20% of patients
- Most common:
  - 1) Central nervous system
  - 2) Gastrointestinal
  - 3) Hepatic
- Dermatologic: 13% increased odds with each additional day

Hospital

- 16% of patients
- Most common:
  - 1) Gastrointestinal
  - 2) Renal
  - 3) Hematologic abnormalities
- Prolonged hospitalization in 24% of ADE patients

Curran et al. Clin Micro Infect. 2021.

Tamma et al. JAMA Intern Med. 2021.

ADE in Nonindicated Antibiotics

- "The study investigators determined that **287 (19%) of antibiotic regimens were not clinically indicated**, most commonly because of treatment of **asymptomatic bacteriuria** or treatment of noninfectious lower respiratory tract conditions"

287 Nonindicated antibiotic regimens → 56 (20%) were associated with an ADE

Tamma et al. JAMA Intern Med. 2021.

Adverse Drug Events (ADE) Increases with Duration

4%↑
Odds ratio/day

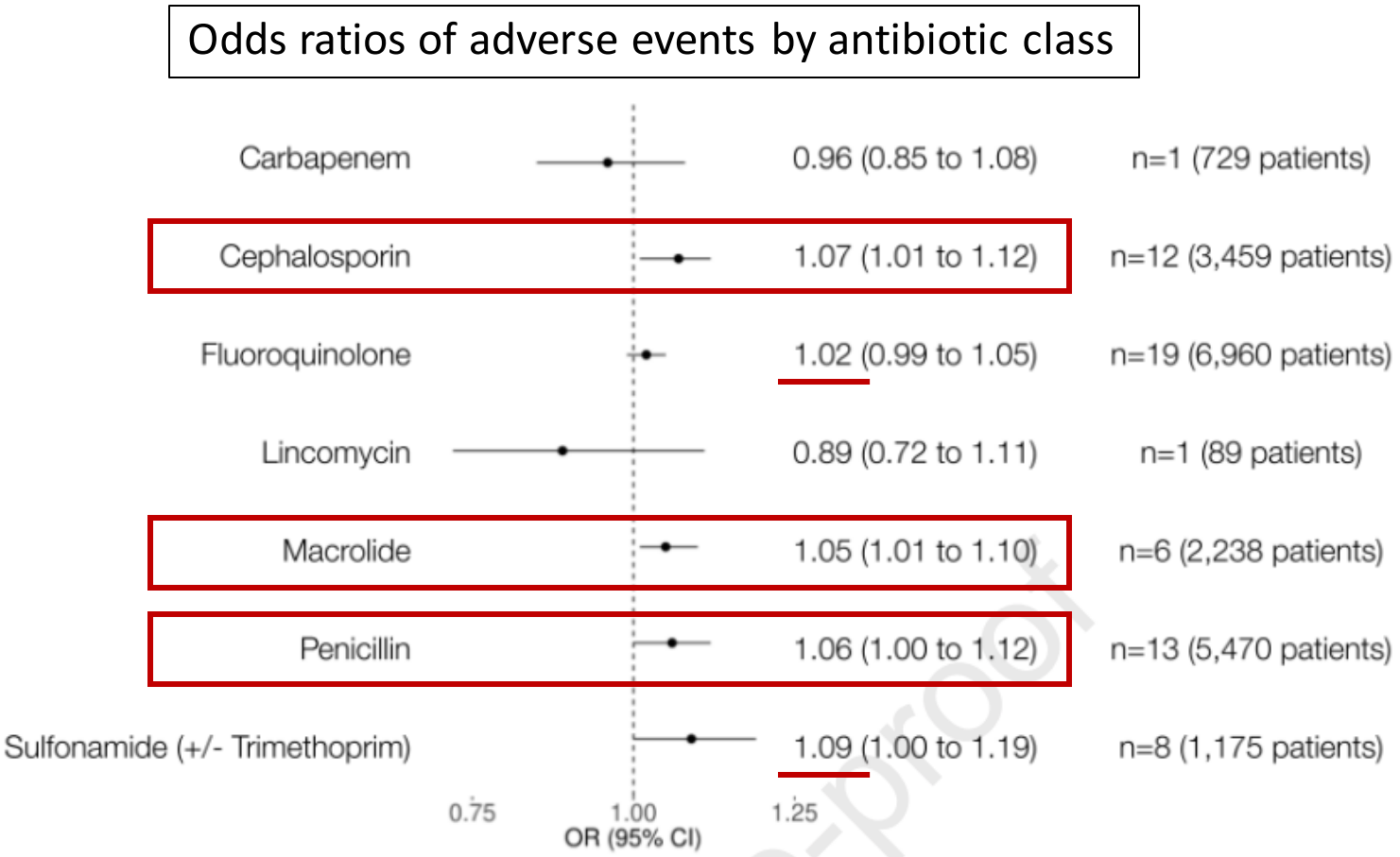
Adverse drug events

9%↑
Odds ratio/day

Severe adverse drug events

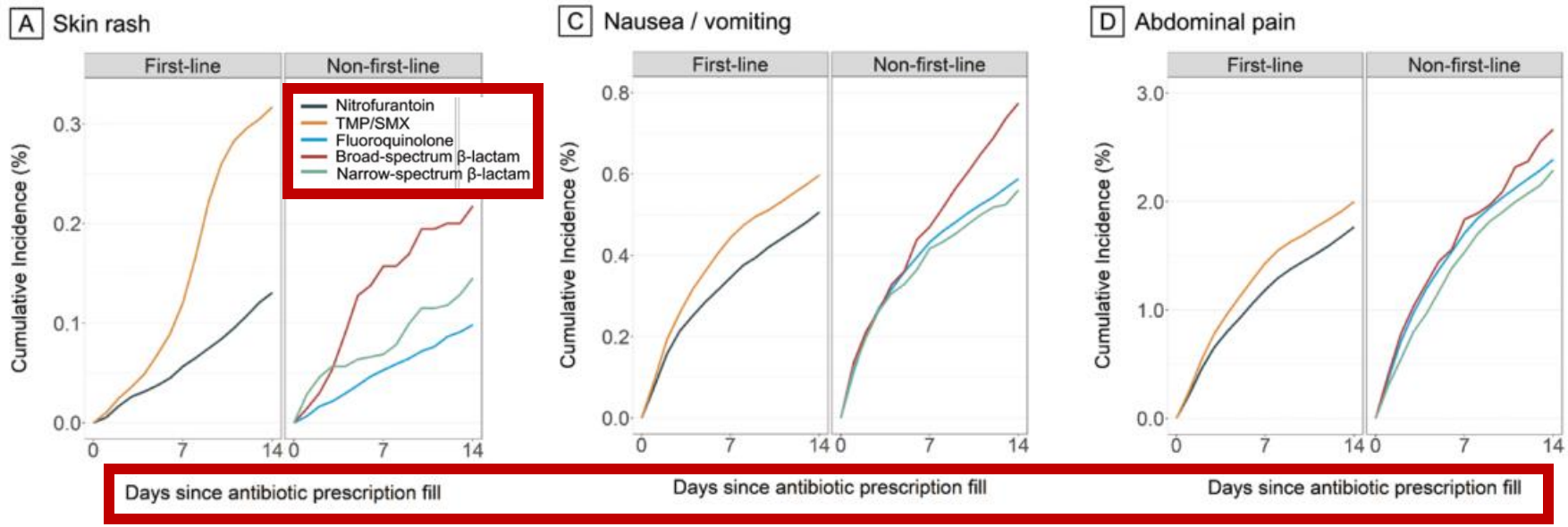
Curran et al. Clin Micro Infect. 2021.

ADEs Vary by Antibiotic Class



Curran et al. Clin Micro Infect. 2021.

ADEs Vary by Antibiotic Class



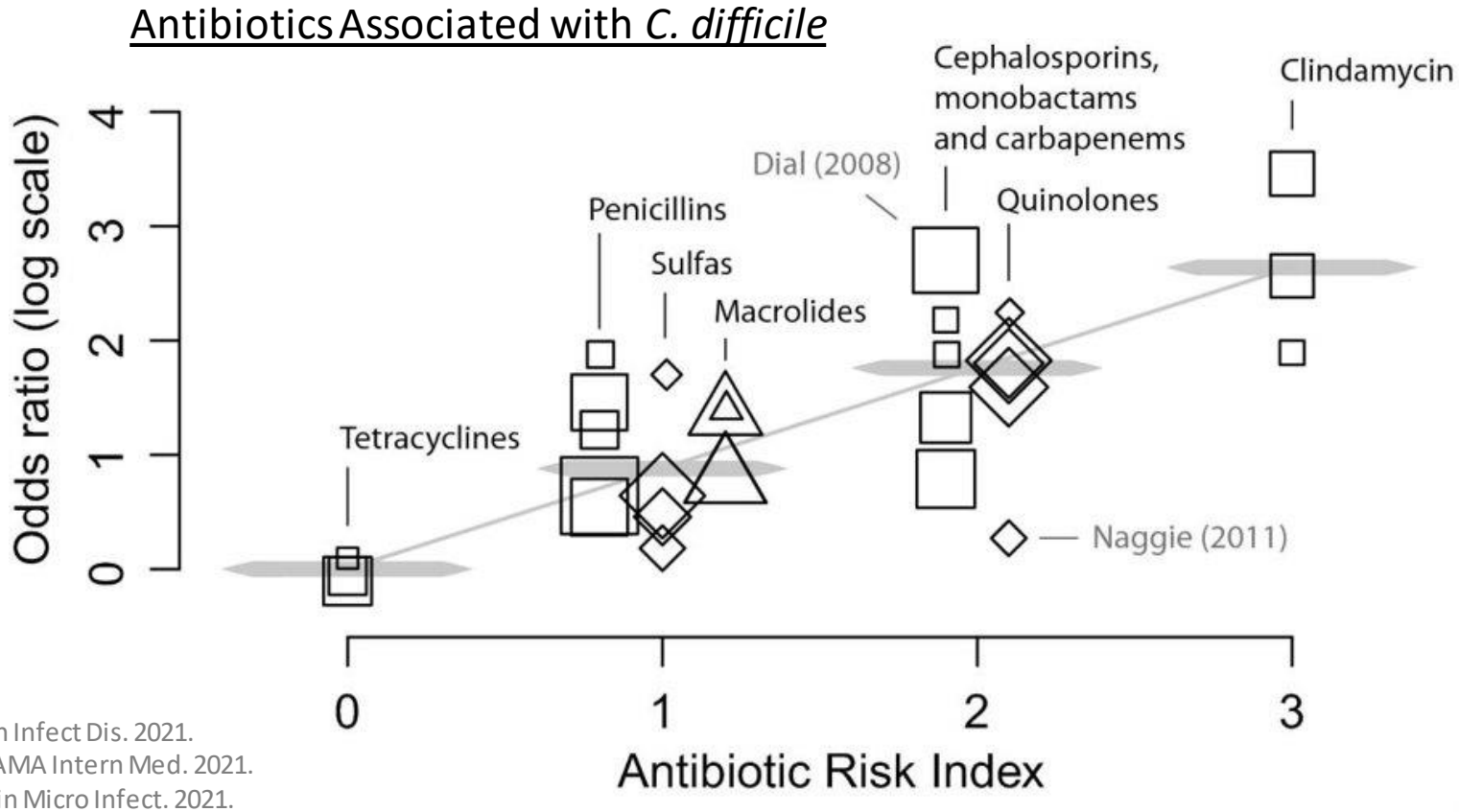
- Increased risks compared to nitrofurantoin

	TMX/SMX	FQ	B-lactams
Hypersensitivity	↑		
Acute renal fail	↑	↑	
Skin rash	↑		↑
Urticaria	↑		
Abdominal pain	↑	↑	↑
Nausea/vomiting	↑	↑	↑

Butler et al. Clin Infect Dis. 2021.

Super Infections

- *Clostridioides difficile* infection
  - 9-13% increase in relative risk with each additional day of therapy



Butler et al. Clin Infect Dis. 2021.
Tamma et al. JAMA Intern Med. 2021.
Curran et al. Clin Micro Infect. 2021.
Brown et al. Antimicrob Agents Chemother. 2013.

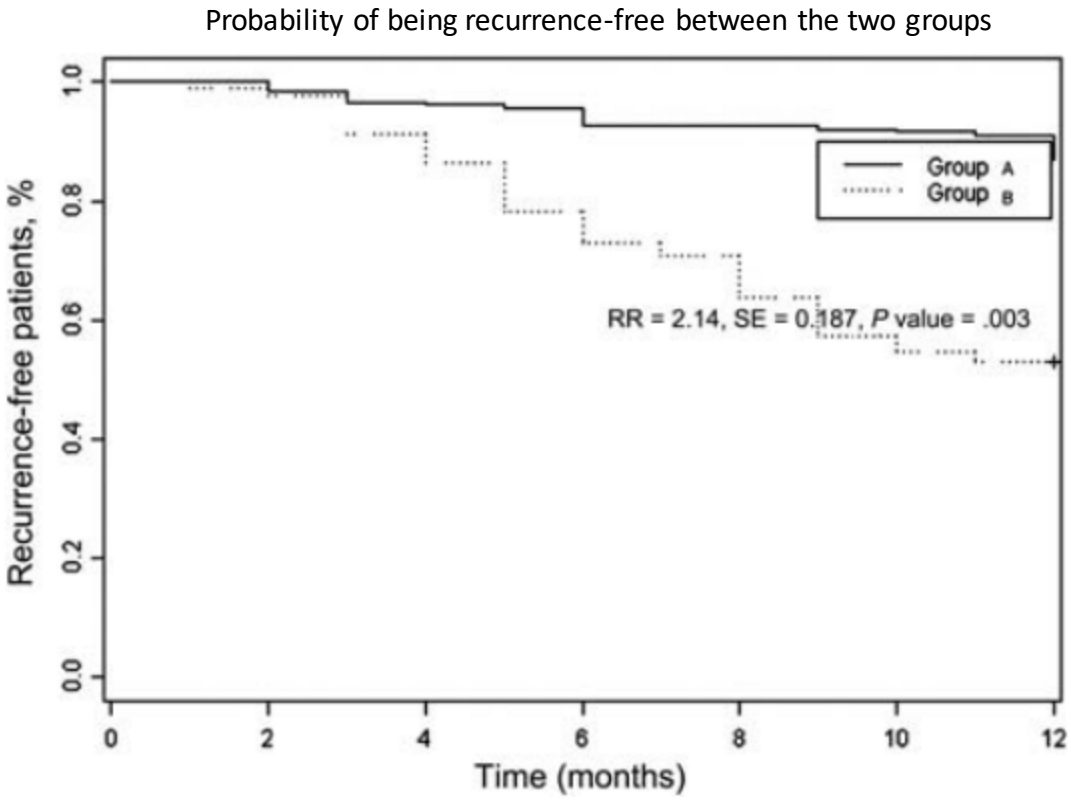
Greater Days and Number of Antibiotics Increases Risk of CDI

Characteristic	CDI positive *n* (%)	CDI negative *n* (%)	Crude hazard ratio[a,b] (95% CI)	Adjusted hazard ratio[a,c,d] (95% CI)
Defined daily doses[e], median (IQR)	14.8 (21.2)	7.2 (12.3)	—	—
<3.0	18 (7)	1502 (15)	Ref	Ref
3.0 to 7.79	49 (20)	3702 (37)	1.1 (.7, 2.1)	1.2 (.7, 2.1)
7.80 to 21.0	89 (37)	2952 (30)	2.9 (1.8, 4.8)	2.8 (1.7, 4.6)
>21.0	85 (35)	1757 (18)	5.3 (3.2, 8.8)	5.3 (3.1, 9.0)
Antibiotic days, median (IQR)[f]	14.0 (23.0)	7.0 (9.0)	—	—
<4	22 (9)	2208 (22)	Ref	Ref
4 to 7	41 (17)	3071 (31)	1.5 (.9, 2.4)	1.4 (.8, 2.4)
8 to 18	87 (36)	3097 (31)	3.4 (2.1, 5.4)	3.0 (1.9, 5.0)
>18	91 (38)	1537 (16)	9.8 (6.0, 16.0)	7.8 (4.6, 13.4)
Number of antibiotics, median (IQR)[f]	3.0 (4.0)	2.0 (2.0)	—	—
1	31 (13)	3744 (38)	Ref	Ref
2	54 (22)	2507 (25)	2.7 (1.8, 4.3)	2.5 (1.6, 4.0)
3 or 4	70 (29)	2505 (25)	3.7 (2.4, 5.7)	3.3 (2.2, 5.2)
5 or more	86 (36)	1157 (12)	11.6 (7.7, 17.4)	9.6 (6.1, 15.1)

Conclusion: CDI patients received greater cumulative doses, numbers, and days of antibiotics relative to non-cases

Stevens V et al. CID 2011;53:42-48.

Treating ASB could increase the risk of subsequent UTI



- Group A: <u>not</u> treated (n=312)
- Group B: treated (n=361)

12 months after enrollment: 41 (14.7%) of patients in non-ASB treated group and 169 (73.1%) in the treated ASB group showed symptomatic UTI

Wagenlehner F, et al. Clin Infect Dis. 2012.
Cai, et al. Clin Infect Dis. 2012.

Antibiotic Exposure and Development of New Resistance

	Cefepime (n=61)	Meropenem (n=103)	Piperacillin- tazobactam (n=108)
Pathogens, n (%)			
Achromobacter species	6 (9.8)	2 (1.9)	1 (1)
Acinetobacter baumannii	12 (19.7)	11 (10.7)	5 (4.9)
Burkholderia cepacia	0 (0)	2 (1.9)	0 (0)
Citrobacter species	3 (4.9)	0 (0)	8 (7.8)
Enterobacter species	8 (13.1)	9 (8.7)	44 (42.7)
Escherichia coli	14 (23.0)	2 (1.9)	10 (9.7)
Klebsiella oxytoca	2 (3.3)	0 (0)	4 (3.9)
Klebsiella pneumoniae	3 (4.9)	4 (3.9)	14 (13.6)
Morganella morganii	0 (0)	0 (0)	0 (0)
Proteus mirabilis	1 (1.6)	1 (1.0)	0 (0)
Providencia species	0 (0)	1 (1.0)	0 (0)
Pseudomonas aeruginosa	11 (18.0)	67 (65.0)	13 (12.6)
Serratia species	0 (0)	0 (0)	8 (7.8)
Stenotrophomonas maltophilia	1 (1.6)	3 (2.9)	0 (0)
Other rare gram-negative pathogen	0 (0)	0 (0)	1 (1.0)

- Bacterial pathogens that developed new resistance
- Urine source = 38%

4% increased risk of new resistance for each additional day of any antipseudomonal beta-lactam exposure

Teshome et al. Pharmacotherapy. 2019.

Drug Interactions

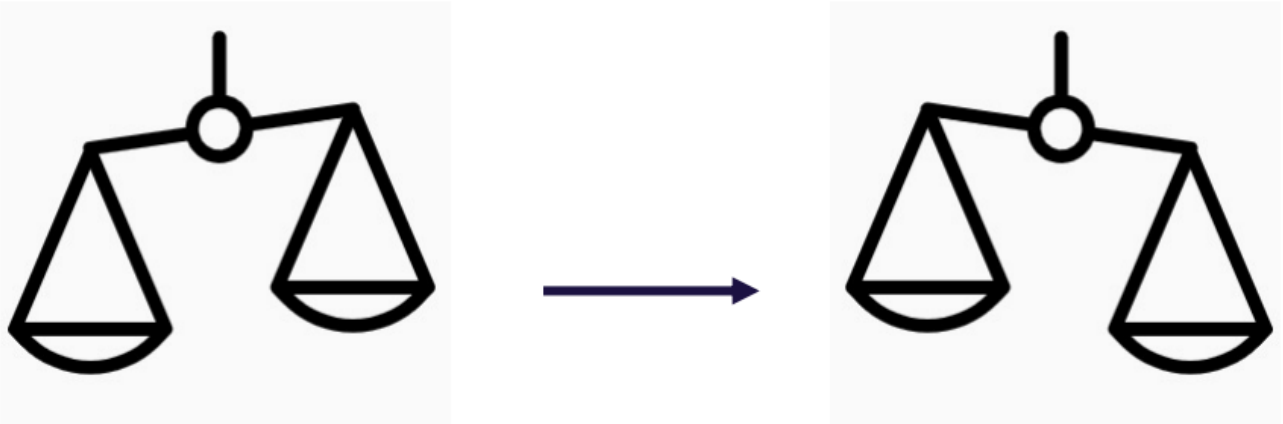
- Warfarin
  - Most significantly: **trimethoprim/sulfamethoxazole****, metronidazole, fluconazole
  - Variable and patient specific: **fluoroquinolones**, macrolides
- Combination of drugs that prolong QTc interval
- Anti-seizure medications
- Statins
- **AND MORE!**

Align Patient Safety and Stewardship

Use data or cases to improve quality and patient safety	Transparency and patient engagement	Hard to completely eliminate→ limit unnecessary exposures to antibiotics
• Without information on testing and prescribing patterns, clinicians may not be aware of their role in inappropriate testing or prescribing	• Openly discuss risks for harms with patients and families • Makes them partners in their own safety	• Shorten duration of therapy • Optimize use of first line agents

Conclusions

- Each additional day of antibiotic therapy is associated with **significant antibiotic harm**
- Antimicrobial-associated ADEs should be considered when **weighing decisions to initiate or discontinue** antibiotic therapy



CSiM | CENTER FOR STEWARDSHIP IN MEDICINE

December 15, 2022

Antibiotic Harms

Whitney Hartlage, PharmD