November 18, 2021

Antibiotic Harms

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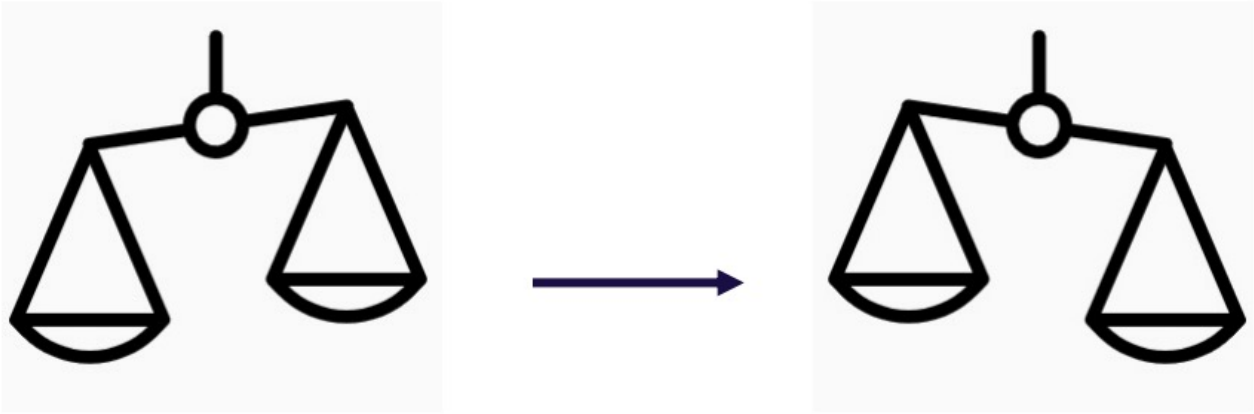
Recap

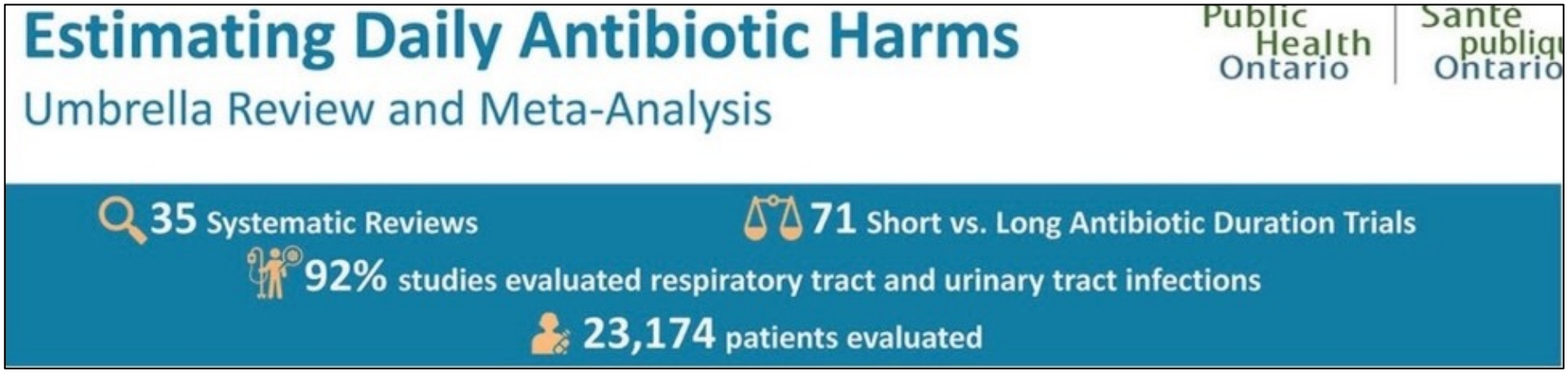


IDSA ASB Guidelines

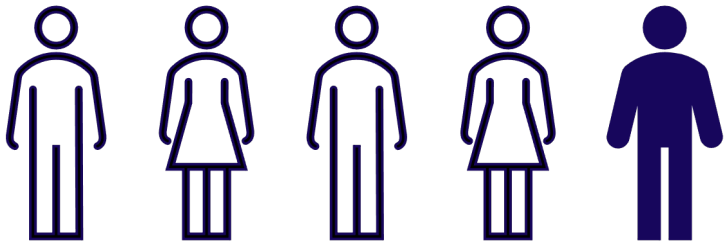
"We make a strong recommendation because there is high certainty for **harm** and low certainty of any benefit from treatment of ASB in older adults"

Nicolle et al. Clin Infect Dis. 2019.

Antibiotic Harms



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

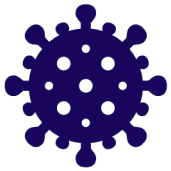


Curran et al. Clin Micro Infect. 2021.

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:
  - Gastrointestinal
  - Renal
  - Hematologic abnormalities

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 ADR

Tamma et al. JAMA Intern Med. 2021.

Adverse Drug Events (ADE) Increases with Duration

4%↑
Odds ratio/day

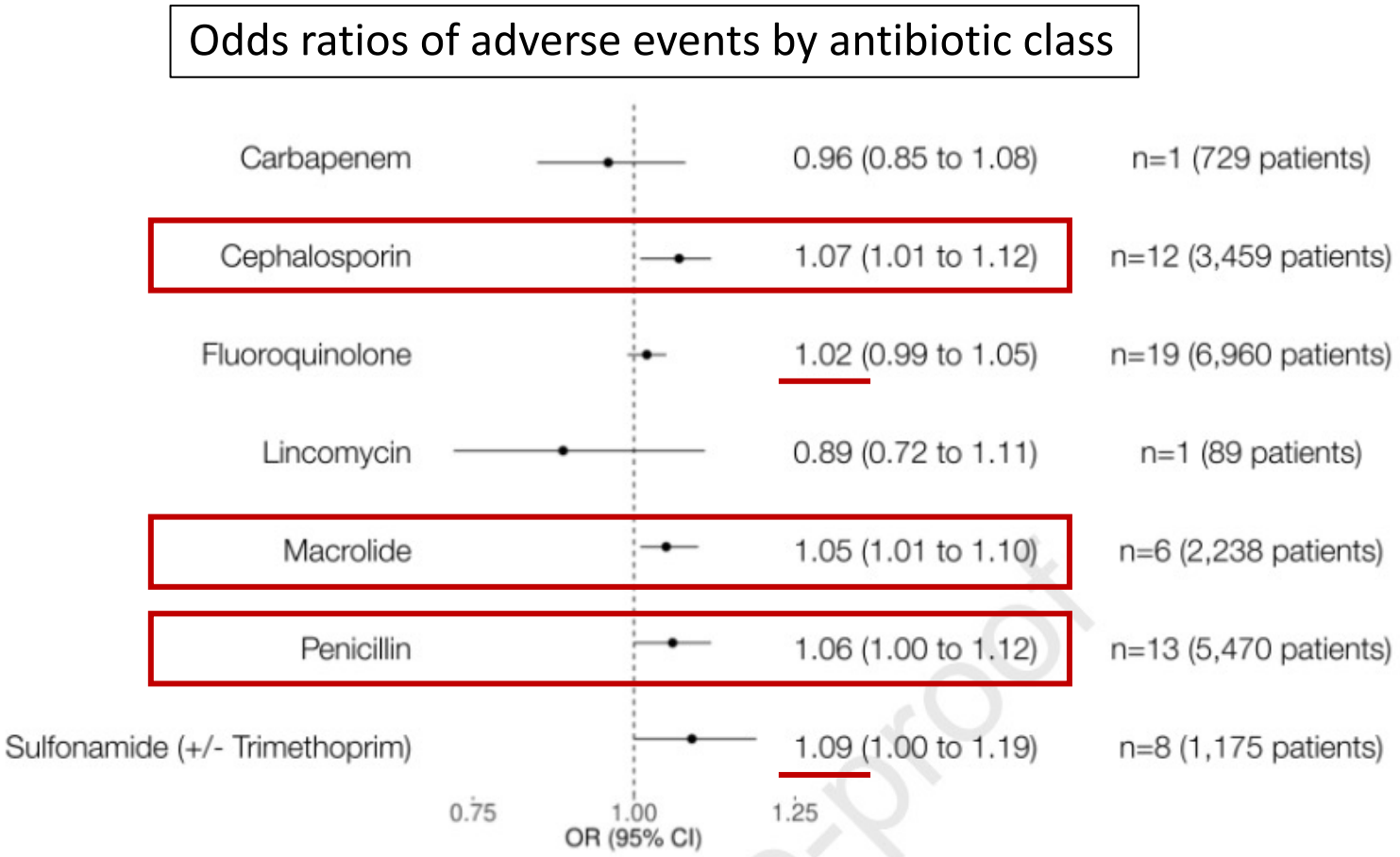
Adverse drug events

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.

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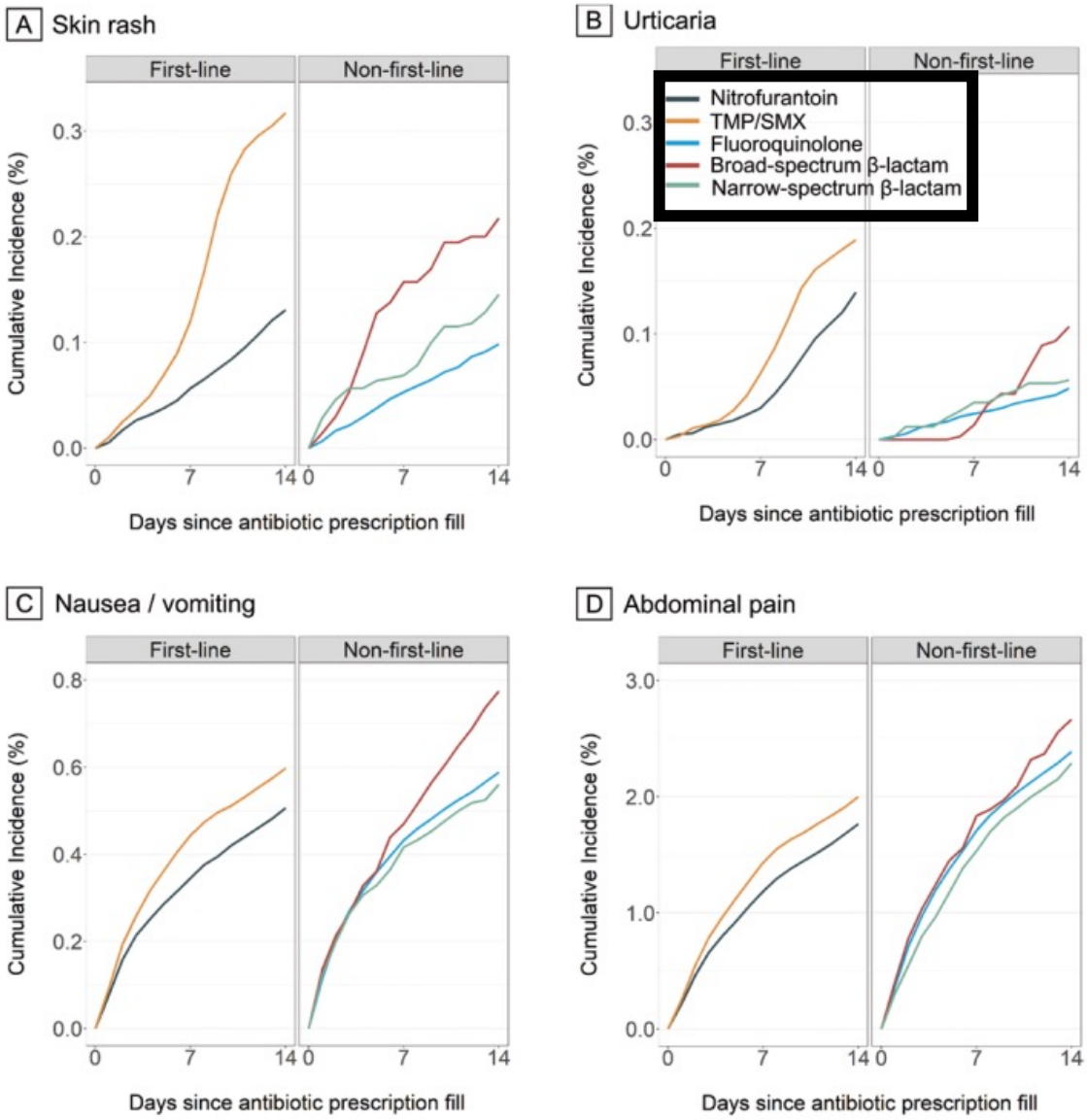


- Increased risks compared to nitrofurantoin
  - **TMP/SMX:** hypersensitivity, acute renal failure, skin rash, urticaria, abdominal pain, N/V
  - **FQ:** acute renal failure, abdominal pain, N/V
  - **B-lactams:** skin rash, abdominal pain, N/V

Butler et al. Clin Infect Dis. 2021.

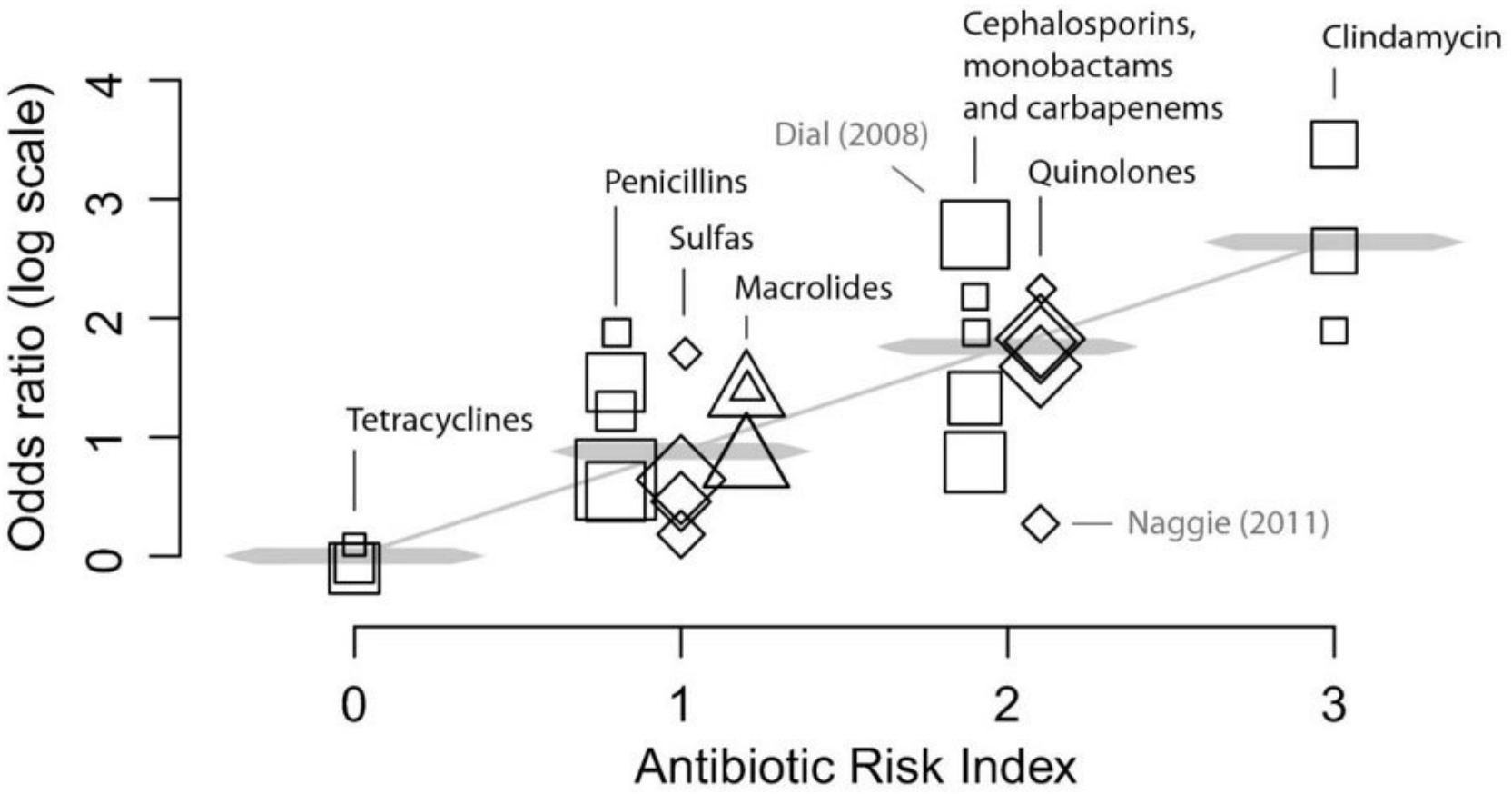
Super Infections

- *Clostridioides difficile* infection
  - 9-13% increase in relative risk with each additional day of therapy
- Candidiasis (4.4%)
  - OR 1.05, 95% CI [0.93 to 1.17]

Outcome	Follow-up, days	Antibiotic Agent[a]	No. of Events	Person-Time, days	Rate per 10 000 Person-Days	Crude HR (95% CI)	Weighted HR (95% CI)
Vaginitis/vulvovaginal candidiasis	30	Nitrofurantoin	3978	6 639 901	5.99	1 [Reference]	1 [Reference]
		TMP/SMX	4335	7 711 026	5.62	.94 (.90–.98)	.98 (.94–1.03)
		Fluoroquinolone	6839	12 265 099	5.58	.93 (.90–.97)	.98 (.94–1.03)
		Broad-spectrum BL	224	300 178	7.46	1.24 (1.09–1.42)	1.32 (1.26–1.37)
		Narrow-spectrum BL	550	743 141	7.40	1.24 (1.13–1.35)	1.30 (1.25–1.35)
		AMX/AMP	144	172 293	8.36	1.39 (1.18–1.64)	1.59 (1.53–1.65)

Butler et al. Clin Infect Dis. 2021.
Tamma et al. JAMA Intern Med. 2021.
Curran et al. Clin Micro Infect. 2021.

Antibiotics Associated with *C. difficile*



Brown K et al. Antimicrob Agents Chemother. 2013;57(5):2326-2332.

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.

Resistance Correlates with Usage

Antibiotic	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant *Staphylococcus aureus* Penicillin-resistant *Streptococcus pneumoniae*	1942 1967
Methicillin	1960	Methicillin-resistant *Staphylococcus aureus*	1960
Extended-spectrum cephalosporins	1980	Extended-spectrum beta-lactamase producing *Escherichia coli*	1983
Imipenem	1985	*Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant *Neisseria gonorrhoeae*	2007
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing *Klebsiella pneumoniae*	2015

CDC. Antimicrobial Resistance. 2020.

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

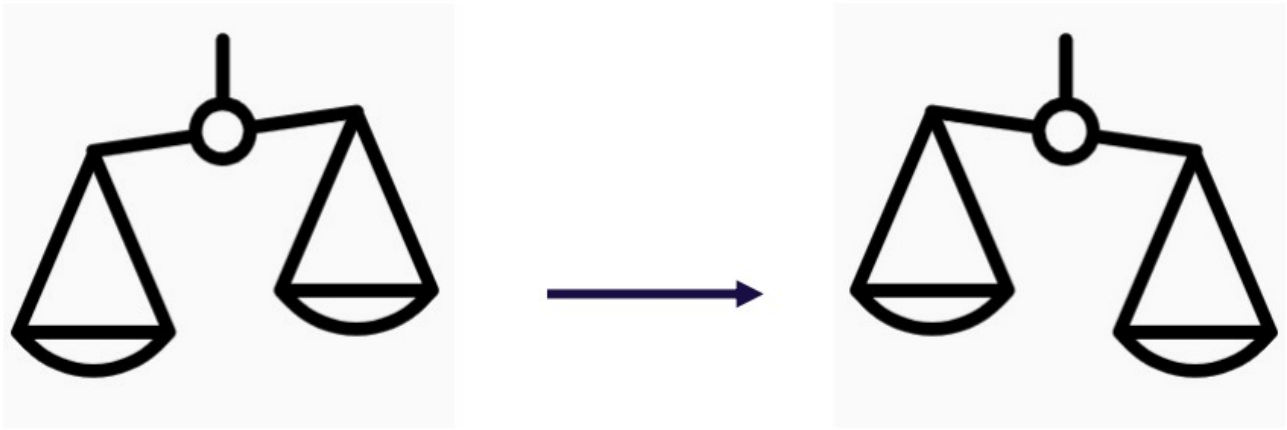
Teshome et al. Pharmacotherapy. 2019.

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!**

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



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