Antibiotics: Resistance, Interactions, Adverse Effects, Oh My!

BETH LOECKER, PHARMD

Google images. Pinterest.com

Financial Disclosure

- “I have had no financial relationship over the past 24 months with any commercial sponsor with a vested interest in this presentation”

Objectives (pharmacist)

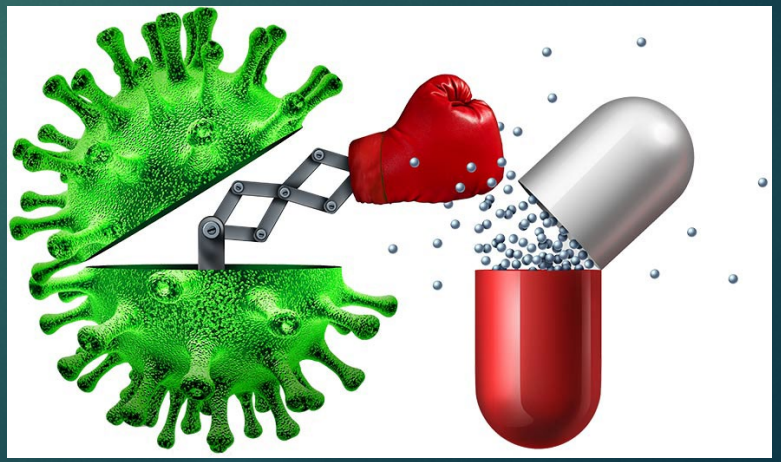
- Identify emerging resistance and which antibiotics to use empirically
- Discuss drug-drug interactions with antibiotics and how to avoid them or provide optimal treatment
- Identify updates to the *Clostridium difficile* guidelines and treatment options
- Discuss up and coming NEW antibiotics options

Objectives (technicians)

- Identify resistance microorganism and antibiotics to treat them
- Identify antibiotics with potential drug-drug interactions
- Identify updates to the *Clostridium difficile* guidelines and treatment options
- Discuss up and coming NEW antibiotics options

Emerging Resistance

ANTIBIOTICS ARE UNLIKE ANY OTHER DRUG, IN THAT THE USE OF THE DRUG IN ONE PATIENT CAN COMPROMISE ITS EFFICACY IN ANOTHER PATIENT!



https://www.antibioticresearch.org.uk/wp-content/uploads/2019/07/antibiotic-resistant-bacteria.jpg

Resistance in the US

- Definition: when microorganisms develop the ability to defeat the drugs that were designed to kill them
- 2.8 million antibiotic-resistance infections each year
- More than 35,000 deaths as a result
  - Decreased by 18% since first resistance report in 2013

https://www.cdc.gov/drugresistance/about.html

2019 Antibiotic Resistance US Report

- 18 microorganisms in the report
- Urgent, serious, and concerning threats + a watch list
  - **<u>Urgent</u>**
    - Carbapenem-resistant *Acinetobacter*
    - *Candida auris*
    - *Clostridium difficile*
    - Carbapenem-resistant Enterobacteriaceae (CRE)
    - Drug-resistant *Neisseria gonorrhoeae*

www.cdc.gov/DrugResistance/Biggest-Threats.html

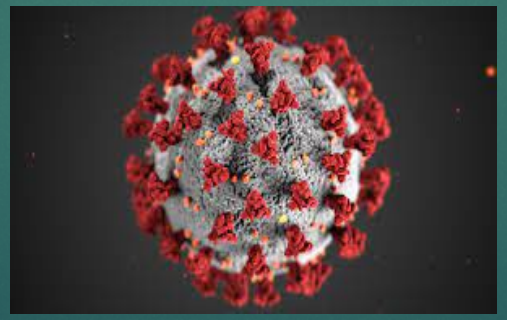
2019 Antibiotic Resistance US Report

- **Serious Threats**
  - Drug-resistance *Candida*
  - Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
  - Vancomycin-resistant *Enterococci* (VRE)
  - Multidrug-resistance *Pseudomonas aeruginosa*
  - Methicillin-resistance *Staphylococcus aureus* (MRSA)
  - Drug-resistant *Streptococcus pneumonia*

www.cdc.gov/DrugResistance/Biggest-Threats.html

A VIRUS did what!?!?

- New data (lost progress in the war against resistance)
  - 15% increase in antibiotic-resistant infections and deaths in hospitals in 2020
  - ~80% of pts hospitalized with COVID-19 (A VIRUS) received an abx between March-October 2020



FDA.gov

https://www.cdc.gov/media/releases/2022/s0712-Antimicrobial-Resistance.html
https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf

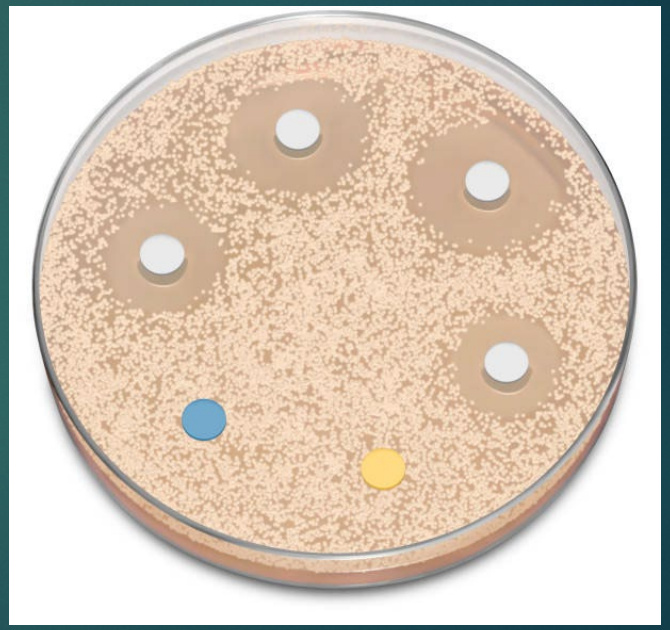
A VIRUS did what!?!?

- Carbapenem-resistance *Acinetobacter*: 78% ↑
- Multidrug-resistant *Pseudomonas aeruginosa*: 32% ↑
- ESBL-producing Enterobacterales: 32% ↑
- Vancomycin-resistant *Enterococcus* (VRE): 14% ↑
- Methicillin-resistant *Staphylococcus aureus* (MRSA): 13% ↑
- *Candida auris*: 60% ↑

- Only healthcare-associated pathogen to ***improve***: *Clostridioides difficile*

https://www.cdc.gov/media/releases/2022/s0712-Antimicrobial-Resistance.html
https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf

South Dakota's statewide antibiogram (2018)



https://media.gettyimages.com/photos/bacterial-culture-a-bacterial-culture-is-a-laboratory-technique-that-picture-id648918062?k=20&m=648918062&s=612x612&w=0&h=18VR90PTLrJsWkUZ3aWBHvj3GjrWtDu50UHjioroHCM=

Gram negative organisms						
	Salmonella spp.	Klebsiella pneumoniae	Pseudomonas aeruginosa	Escherichia coli	Extended spectrum beta-lactamase (ESBL) E. coli‡	Proteus spp.
Antibiotic	**% Susceptible and (n) number of isolates tested**					
Ertapenem		100(2574)		9915564)	100(403)	100(862)
Imipenem		100(1154)	93(723)	99(6720)		83(54)
Meropenem		96(2713)	95(1862)	99(16447)	100(48)	100(1016)
Amoxicillin/Clavulanic acid		96(287)		88(1914)		100(53)
Ampicillin/Sulbactam		88(2486)		67(15394)		86(1182)
Cefazolin		95(3218)		90(19488)		90(1174)
Cefepime		97(3152)	94(2056)	96(18975)		97(1138)
Cefotaxime		96(183)		93(1191)		98(54)
Ceftazidime		98(2485)	94(1495)	96(15408)		98(1182)
Ceftriaxone	97(58)	97(3238)		95(19733)		97(1182)
Ampicillin	87(177)	1(1651)		60(19664)		81(1180)
Piperacillin/Tazobactam		96(3246)	98(2142)	96(19605)	61(106)	98(1181)
Ciprofloxacin	92(177)	97(3300)	88(2169)	85(19943)	20(451)	73(1182)
Levofloxacin	100(41)	98(3181)	86↑(2098)	85(19560)	20(451)	78(1138)
Tobramycin		98(3195)	98(2162)	94(19580)		92(1182)
Gentamicin		98(3284)	93(2163)	94(19855)	77(438)	91(1180)
Nitrofurantoin*		37(2395)		97(15003)	90(438)	0(360)
Trimethoprim/Sulfamethoxazole		93(3232)		81(19749)	45(451)	80(1179)
Tetracycline		85(959)		81(5879)		
	>5% increase in susceptibility from 2013			>5% decrease in susceptibility from 2013		

↓Denotes a 10% or greater decrease change in susceptibility compared to data from 2013
↑Denotes a 10% or greater increase change in susceptibility compared to data from 2013
*Urine isolates only
CLSI recommends reporting data only if 30 or more isolates analyzed, less than 30 isolates are reported for completeness, but may not be statistically valid

Gram Negatives

- ***E coli***
  - 96%: Zosyn
  - 95%: ceftriaxone
  - 90%: cefazolin
  - 85%: cipro/levofloxacin
  - 81%: trimeth/sulfa
- ***Pseudomonas aeruginosa***
  - 98%: Zosyn
  - 95%: meropenem
  - 94%: cefepime/ceftazidime
  - 88%: ciprofloxacin

https://doh.sd.gov/diseases/hai/2015antibiogram.aspx

Gram positive organisms

Antibiotic	Staphylococcus aureus†	Methicillin-susceptible S. aureus (MSSA)	Methicillin-resistant S. aureus (MRSA)	Streptococcus pyogenes	Streptococcus agalactiae	Streptococcus pneumoniae^	Streptococcus pneumoniae (meningitis)	Streptococcus pneumoniae (non-meningitis)	Enterococcus faecalis	Enterococcus faecium
	% Susceptible and (n) number of isolates tested									
Amoxicillin/Clavulanic acid										
Cefepime										
Cefotaxime						100(29)	86(133)	98(133)		
Ceftriaxone				100(50)	100(101)	95(39)	92(512)	97(512)		
Ampicillin					100(154)				99(2294)	68↑(584)
Oxacillin‡	55(772)	100(3566)	0(874)							
Penicillin‡		35(1462)	0(728)	100(89)	99(220)	74(38)	66(509)	97(509)	98(2753)	56(674)
Ciprofloxacin										
Levofloxacin				98(61)	100(288)	99(551)				
Clindamycin	80(884)	80(3641)	68(2041)	90↑(59)	41(343)	84(505)				
Daptomycin	100(836)	99(261)	97(159)						99(304)	
Erythromycin	47(885)	68(3581)	14(1836)	88(59)		44(551)				
Gentamicin Synergy									72(2927)	86(691)
Linezolid	100(936)	100(1540)	100(851)		100(118)	100(64)			96(3134)	98(723)
Nitrofurantoin*	100(147)	100(3521)	100(1858)						99(3161)	74(719)
Rifampin	100(679)	99(1278)	99(657)							
Trimethoprim/Sulfamethoxazole	98(936)	98(3620)	97(1873)			76(497)				
Tetracycline	91(846)	94(3700)	95(1912)		18(116)	79(170)			23(3110)	22↓(713)
Vancomycin	100(939)	100(3702)	100(1912)	100(86)	100(470)	100(511)			99(3268)	72↑(728)
	>5% increase in susceptibility from 2013					>5% decrease in susceptibility from 2013				

↓Denotes a 10% or greater decrease change in susceptibility compared to data from 2013
↑Denotes a 10% or greater Increase change in susceptibility compared to data from 2013
*Urine isolates only
†From laboratories which did not separate MRSA and MSSA. Data included in this column is not included in the MSSA or MRSA columns.
^ From laboratories which did not separate meningitis breakpoints. Data included in this column for cefotaxime, ceftriaxone, and penicillin is not included in the meningitis or non-meningitis columns.
‡Only reported oxacillin and penicillin for Staph. aureus based on CLSI guidelines
CLSI recommends reporting data only if 30 or more isolates analyzed, less than 30 isolates are reported for completeness, but results may not be statistically valid

Gram Positives

- ***Streptococcus pneumoniae***
  - 99%: levofloxacin
  - 95%: ceftriaxone
  - 44%: erythromycin
- ***Enterococcus faecalis***
  - 99%: ampicillin
  - 99%: nitrofurantoin
  - 99%: vancomycin
- ***Enterococcus faecium***
  - 68%: ampicillin
  - 74%: nitrofurantoin
  - 72%: vancomycin

https://doh.sd.gov/diseases/hai/2015antibiogram.aspx

Resistance in Urinary Tract Infections

- **Most common pathogens:**
  - ** *Escherichia coli* (E coli) ** (75-95%)**
  - ***Proteus mirabilis***
  - ***Klebsiella pneumonia***
  - ***Staphylococcus saprophyticus***

Livescience.com

- Optimal **empiric treatment** for E coli based upon local antibiogram
  - **<u>Cephalexin</u> 250 to 500 mg every 6 hours for 5 to 7 days (90% cefazolin)**
  - **<u>Nitrofurantoin</u> 100 mg twice daily; treat females for 5 days and males for 7 days (97%)**
  - **Less optimal options**
    - **Trimethoprim-sulfamethoxazole (81%), ciprofloxacin (85%), levofloxacin (85%)**

Gupta et al. IDSA Practice Guidelines for UTIs. CID 2011:52 (1 March).
Lexi-Comp Online Database (2022).

Gram negative resistance: Extended Spectrum Beta-Lactamase (ESBL)

- enzymes that inactivate most penicillins, cephalosporins, and aztreonam
- Rates:
  - 2017: estimated 197,400 cases of ESBL Enterobacterales in hospitalized patients
  - 9,100 estimated deaths in US
- Oral options
  - Nitrofurantoin
  - Fosfomycin
- IV options
  - Amikacin
  - carbapenems

(https://www.cdc.gov/hai/organisms/ESBL.html)

Resistance in Skin and Soft Tissue Infections

- **Most common pathogens: *Staphylococcus* and *Streptococcus***
- **Treatment for Methicillin Resistant *Staphylococcus aureus***
  - *Oral*
    - ***Linezolid 600 mg po every 12 hours***
    - ***Clindamycin 300-450 mg po every 6 hours***
    - ***doxycycline or minocycline 100 mg po every 12 hours***
    - ***Trimethoprim-sulfamethoxazole 1-2 DS tablets every 12 hours***
  - *IV*
    - ***Vancomycin (dosed based on patient specific kinetics)***
    - ***Linezolid 600 mg IV/oral every 12 hours***
    - ***Daptomycin 4-6 mg/kg IV every 24 hours***
    - ***Ceftaroline 600 mg IV every 12 hours***

Stevens et al. IDSA Practice Guidelines for SSTIs. CID 2014:59 (15 July).
Lexi-Comp Online Database (2022).

Patient Case (UTI)

- LG is an 89 y/o female that presents to the clinic with a symptomatic UTI. She has no drug allergies and no history of UTIs or antibiotics in the last 5 years.
- Which antibiotic would be the best option for empiric UTI therapy?

- A) trimethoprim/sulfamethoxazole
- B) cephalexin

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- **B) cephalexin**

Which microorganism often has resistance in the US?

- A) *Staphylococcus aureus*
- *B) Candida albicans*
- C) *Streptococcus pyogenes*

Which microorganism often has resistance in the US?

- **A) *Staphylococcus aureus***
- ***B) Candida albicans***
- ***C) Streptococcus pyogenes***

Antibiotic Drug Interactions/Adverse Effects

- sucralfate binding + antibiotics
- Linezolid + medications that affect serotonin
- Daptomycin + statins
- Trimethoprim-sulfamethoxazole + ACEIs
- Penicillin allergies

Sucralfate + Antibiotics

- Separate administration by at least 2 hours with other medications
- Often difficult to do given sucralfate is often prescribed 4x per day
- Specific antibiotics affected:
  - Quinolones
  - Tetracyclines

American-time.com

Lexi-Comp Online Database (2022)

Linezolid drug interactions with potential for serotonin syndrome

- Linezolid
  - Lipophilic features makes for excellent tissue penetration including the central nervous system
  - Weak reversible non-selective monoamine oxidase (MAO) inhibitory effects at therapeutic serum concentrations
    - MAO is part of the metabolism of monoamine neurotransmitters, and its inhibition may potentially lead to excess serotonin in the CNS and the occurrence of serotonin syndrome (SS)

Gatti, M., Raschi, E. & De Ponti, F. Serotonin syndrome by drug interactions with linezolid: clues from pharmacovigilance-pharmacokinetic/pharmacodynamic analysis. Eur J Clin Pharmacol 77, 233–239 (2021). https://doi.org/10.1007/s00228-020-02990-1

Serotonin Syndrome

- Inhibition of serotonin reuptake transporter (SERT) which causes an accumulation of serotonin in the synaptic cleft and overstimulation of 5-HT2A receptors
- Typically presents within 24-hours
- Mild to LIFE-THREATENING
- Symptoms:
  - Hypertension and tachycardia
  - Mydriasis, diaphoresis, shivering, tremor, myoclonus, and hyperreflexia
  - Hyperthermia (104F), hyperactive bowel sounds, horizontal ocular clonus, mild agitation, hyper vigilance, and pressured speech
  - Delirium and muscle rigidity, seizures, rhabdomyolysis

Jacqueline Volpi-Abadie, Adam M. Kaye and Alan David Kaye. Serotonin Syndrome. Ochsner Journal December 2013, 13 (4) 533-540

European Journal of Clinical Pharmacology (2021) 77:233–239
https://doi.org/10.1007/s00228-020-02990-1

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Serotonin syndrome by drug interactions with linezolid: clues from pharmacovigilance-pharmacokinetic/pharmacodynamic analysis

Milo Gatti[1] · Emanuel Raschi[1] · Fabrizio De Ponti[1]

Received: 15 July 2020 / Accepted: 1 September 2020 / Published online: 8 September 2020

“Two-step” evaluation

- Serotonergic agent concomitantly reported with linezolid >/= 5 cases of serotonin syndrome (SS)

- Step 1:
  - Two indexes:
    - 1) proportion of SS reports as compared with overall number of reports
    - 2) mean number of drug-drug interactions (DDIs) based on concomitant serotonergic agents recorded in SS reports

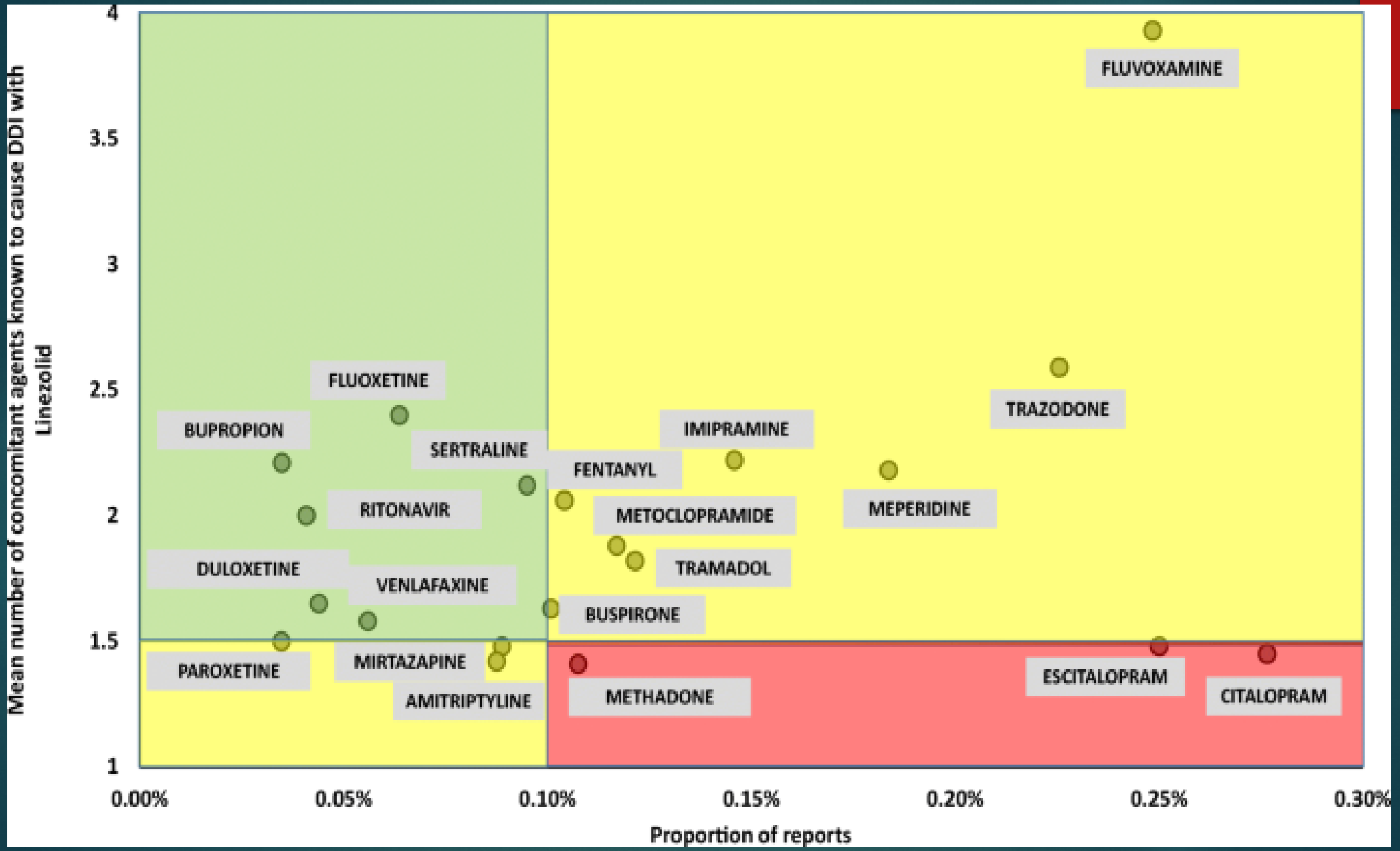
- Step 2: PK/PD indexes were evaluated

Gatti, M., Raschi, E. & De Ponti, F. Serotonin syndrome by drug interactions with linezolid: clues from pharmacovigilance-pharmacokinetic/pharmacodynamic analysis. Eur J Clin Pharmacol 77, 233–239 (2021). https://doi.org/10.1007/s00228-020-02990-1

Three zones

- **RED** zone: medications with high proportion of SS reported and low mean number of DDIs
- **YELLOW** zone: medications with high proportion of SS reports coupled with high mean number of DDIs or low proportion of SS reports coupled with low mean number of DDIs
- **GREEN** zone: medications with low proportion of SS reports and high mean number of DDIs

Gatti, M., Raschi, E. & De Ponti, F. Serotonin syndrome by drug interactions with linezolid: clues from pharmacovigilance-pharmacokinetic/pharmacodynamic analysis. Eur J Clin Pharmacol 77, 233–239 (2021). https://doi.org/10.1007/s00228-020-02990-1



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Daptomycin + Statins

- Incidence of **statin**-induced myopathy or CPK elevation greater than 10 times the ULN = 0.08-0.09%
- Incidence of **daptomycin**-induced myositis with CPK elevation greater than 4 times the ULN = 0.2%
- Current package insert recommends the temporary suspension of statins in patients receiving daptomycin
- Retrospective review 5 studies

Kido, K., Oyen, A., Beckmann, M., Brouse, S. Musculoskeletal toxicities in patients receiving concomitant statin and daptomycin therapy. AM J Health-Syst Pharm. 2019; 76: 206-10.

Study 1 (Berg et al.)

- Daptomycin alone (n=384)
- Daptomycin + statin (n=63)
- Daptomycin + statin on HOLD (n=51)

- Average dose of daptomycin 5.3 +/- 1 mg/kg/dose

- No significant differences in :
  - Elevation in CPK levels (>336 U/L)
  - Rate of myalgia (2.3% vs 4.8% vs 2%)

- Limitations: low event rates, study size and daptomycin dose

Kido, K., Oyen, A., Beckmann, M., Brouse, S. Musculoskeletal toxicities in patients receiving concomitant statin and daptomycin therapy. AM J Health-Syst Pharm. 2019; 76: 206-10.

Study 2 (Bland et al.)

- Daptomycin alone (n=171)
- Concomitant daptomycin + statin (n=49)

- Average daptomycin dose: 6.78 vs 6.75 mg/kg/day

- No significant difference in:
  - CKP elevation (>1000 U/L) – 5.3% vs 10.2%
  - Musculoskeletal side effects – 6.12% vs 2.92%
  - Discontinuation rate of therapy – 3.51% vs 6.12%

- Limitations: low event rate of primary safety outcomes makes the study susceptible to type 2 error

Kido, K., Oyen, A., Beckmann, M., Brouse, S. Musculoskeletal toxicities in patients receiving concomitant statin and daptomycin therapy. AM J Health-Syst Pharm. 2019; 76: 206-10.

Study 3 (McConnell et al.)

- Total number of patients on >/= 48 hours of daptomycin – 233
  - 53 of these patients were also on statin
- Median daptomycin doses: 6 mg/kg/day vs 5.9 mg/kg/day
- Findings but **NOT** significant:
  - Great percentage of CPK elevation (3xULN or if above baseline at initiation 5xULN) – 5.7% vs 1.1%
  - BUT fewer patients died – 17.2% vs 9.4%
- Limitations: CPK elevation was lower than estimated and need for more power to prevent type 2 error

Kido, K., Oyen, A., Beckmann, M., Brouse, S. Musculoskeletal toxicities in patients receiving concomitant statin and daptomycin therapy. AM J Health-Syst Pharm. 2019; 76: 206-10.

Study 4 (Lehman et al.)

- Daptomycin alone (n = 3471)
- Daptomycin + statin (n = 902)

- Significant finding:
  - Incidence of CPK elevation (4.4% vs 2.9%)
- Non-significant finding:
  - Myalgia event rates

- Limitations: study had few details describing pt population, length of therapy, dosages, and statin type

Kido, K., Oyen, A., Beckmann, M., Brouse, S. Musculoskeletal toxicities in patients receiving concomitant statin and daptomycin therapy. AM J Health-Syst Pharm. 2019; 76: 206-10.

Study 5 (Parra-Ruiz et al.)

- Daptomycin alone (n = 36)
- Daptomycin + statin (n = 68)

- Average dose: 8.1 mg/kg/day vs 7.8 mg/kg/day

- Findings (not significant):
  - Grade 2 CPK elevation as defined per WHO: 10% vs 8%

Kido, K., Oyen, A., Beckmann, M., Brouse, S. Musculoskeletal toxicities in patients receiving concomitant statin and daptomycin therapy. AM J Health-Syst Pharm. 2019; 76: 206-10.

Conclusion

- Discontinuation of statin therapy during daptomycin **may not be necessary** based upon lack of evidence of clinically significant CPK elevation or myalgia
- Bland et al had more **obese pts** in the concomitant group yet did NOT find clinical significant differences
- McConnell et all had **older patients** in the concomitant group yet did NOT find clinical significant differences
- Shorter durations (</= 7 days) have minimal risk for CPK elevation
- Continue concomitant therapy unless there is symptomatic evidence of myalgia and CPK elevation or clinically significant CPK elevation (>/= 10xULN) in asymptomatic patients

Kido, K., Oyen, A., Beckmann, M., Brouse, S. Musculoskeletal toxicities in patients receiving concomitant statin and daptomycin therapy. AM J Health-Syst Pharm. 2019; 76: 206-10.

Trimethoprim-sulfamethoxazole (TMP-SMX) + anti-hypertensives

- TMP-SMX is often used in elderly patients to treat UTIs
- Trimethoprim: has structural and pharmacological similarities to the potassium-sparing diuretic amiloride and reduces urinary potassium excretion by approximately 40%
- 2010 population-based study: ~7-fold increased risk of hyperkalemia-associated hospitalizations when comparing amoxicillin vs TMP-SMX
- **Avoid combining TMP-SMX with**:
  - **angiotensin II receptor blockers (ARBs)**
  - **angiotensin-converting enzymes inhibitors (ACEs)**
  - **spironolactone**
- AVOID concomitant use when possible but if not possible consider close monitoring of potassium levels

Antoniou T, Gomes T, Juurlink DN,et al. Trimethoprim-sulfamethoxazole-induced hyperkalemia in patients receiving inhibitors of the renin-angiotensin system: a population-based study. Arch Intern Med. 2010 Jun 28;170(12):1045-9.
Lexi-Comp Online Database (2022)

The “penicillin allergy”

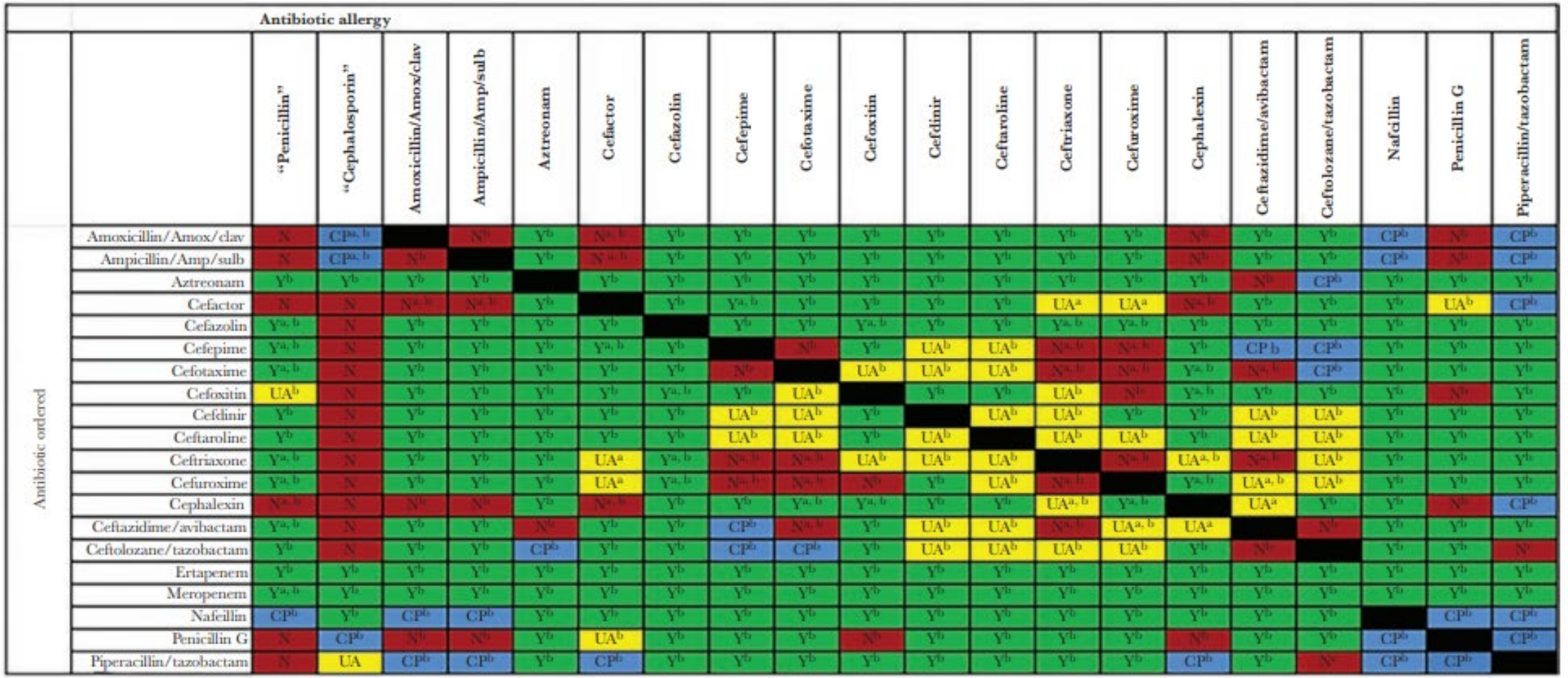
- 10% of the US population reports having a penicillin allergy
- Fewer than 1% of the population has a TRUE IgE-mediated reactions
- 80% of patients with an IgE-mediated reaction lost their sensitivity after 10 years
- Broad-spectrum antibiotics are often used as an alternative
  - Higher healthcare costs
  - Increased risk for resistance
  - Suboptimal treatment

https://www.cdc.gov/antibiotic-use/community/pdfs/penicillin-factsheet.pdf

Cross-reactivity of antibiotic allergies

- Clinically significant immunologically mediated cross-reactivity among ß-lactams is associated with R-group side chain homology
- ß-lactam antibiotics with dissimilar side chains = lower rates of cross-reactivity
- Study: single-center, retrospective cohort study analyzed the impact of implementation of cross-reactivity chart for patients with pneumonia
  - January 2017 to October 2018
  - **Primary outcome**: utilization of ß-lactam antibiotics
    - Significantly greater use in intervention cohort (70.4% vs 89.3%; P <.001)
  - No difference in **overall allergic reactions** (2.4% vs 1.6%; P = .738)
  - No difference in **ß-lactam abx reactions** (1.3% vs 0.9%; P = .703)
  - **Healthcare-onset *C difficile*** decreased (1.2% vs 0.2%; P = .032)

Curtis D Collins, et al. Antibiotic Use in Patients With β-Lactam Allergies and Pneumonia: Impact of an Antibiotic Side Chain–Based Cross-Reactivity Chart Combined With Enhanced Allergy Assessment, Open Forum Infectious Diseases, Volume 9, Issue 1, January 2022, ofab544, https://doi.org/10.1093/ofid/ofab544



Antibiotic ordered	Antibiotic allergy: "Penicillin"	"Cephalosporin"	Amoxicillin/Amox/clav	Ampicillin/Amp/sulb	Aztreonam	Cefactor	Cefazolin	Cefepime	Cefotaxime	Cefoxitin	Cefdinir	Ceftaroline	Ceftriaxone	Cefuroxime	Cephalexin	Ceftazidime/avibactam	Ceftolozane/tazobactam	Nafcillin	Penicillin G	Piperacillin/tazobactam
Amoxicillin/Amox/clav	N	CP[a, b]		N[b]	Y[b]	N[a, b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N[b]	Y[b]	Y[b]	CP[b]	N[b]	CP[b]
Ampicillin/Amp/sulb	N	CP[a, b]	N[b]		Y[b]	N[a, b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N[b]	Y[b]	Y[b]	CP[b]	N[b]	CP[b]
Aztreonam	Y[b]	Y[b]	Y[b]	Y[b]		Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N[b]	CP[b]	Y[b]	Y[b]	Y[b]
Cefactor	N	N	N[a, b]	N[a, b]	Y[b]		Y[b]	Y[a, b]	Y[b]	Y[b]	Y[b]	Y[b]	UA[a]	UA[a]	N[a, b]	Y[b]	Y[b]	Y[b]	UA[b]	CP[b]
Cefazolin	Y[a, b]	N	Y[b]	Y[b]	Y[b]	Y[b]		Y[b]	Y[b]	Y[a, b]	Y[b]	Y[b]	Y[a, b]	Y[a, b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]
Cefepime	Y[a, b]	N	Y[b]	Y[b]	Y[b]	Y[a, b]	Y[b]		N[b]	Y[b]	UA[b]	UA[b]	N[a, b]	N[a, b]	Y[b]	CP b	CP[b]	Y[b]	Y[b]	Y[b]
Cefotaxime	Y[a, b]	N	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	N[b]		UA[b]	UA[b]	UA[b]	N[a, b]	N[a, b]	Y[a, b]	N[a, b]	CP[b]	Y[b]	Y[b]	Y[b]
Cefoxitin	UA[b]	N	Y[b]	Y[b]	Y[b]	Y[b]	Y[a, b]	Y[b]	UA[b]		Y[b]	Y[b]	UA[b]	N[b]	Y[a, b]	Y[b]	Y[b]	Y[b]	N[b]	Y[b]
Cefdinir	Y[b]	N	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	UA[b]	UA[b]	Y[b]		UA[b]	UA[b]	Y[b]	Y[b]	UA[b]	UA[b]	Y[b]	Y[b]	Y[b]
Ceftaroline	Y[b]	N	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	UA[b]	UA[b]	Y[b]	UA[b]		UA[b]	UA[b]	Y[b]	UA[b]	UA[b]	Y[b]	Y[b]	Y[b]
Ceftriaxone	Y[a, b]	N	Y[b]	Y[b]	Y[b]	UA[a]	Y[a, b]	N[a, b]	N[a, b]	UA[b]	UA[b]	UA[b]		N[a, b]	UA[a, b]	N[a, b]	UA[b]	Y[b]	Y[b]	Y[b]
Cefuroxime	Y[a, b]	N	Y[b]	Y[b]	Y[b]	UA[a]	Y[a, b]	N[a, b]	N[a, b]	N[b]	Y[b]	UA[b]	N[a, b]		Y[a, b]	UA[a, b]	UA[b]	Y[b]	Y[b]	Y[b]
Cephalexin	N[a, b]	N	N[b]	N[b]	Y[b]	N[a, b]	Y[b]	Y[b]	Y[a, b]	Y[a, b]	Y[b]	Y[b]	UA[a, b]	Y[a, b]		UA[a]	Y[b]	Y[b]	N[b]	CP[b]
Ceftazidime/avibactam	Y[a, b]	N	Y[b]	Y[b]	N[b]	Y[b]	Y[b]	CP[b]	N[a, b]	Y[b]	UA[b]	UA[b]	N[a, b]	UA[a, b]	UA[a]		N[b]	Y[b]	Y[b]	Y[b]
Ceftolozane/tazobactam	Y[b]	N	Y[b]	Y[b]	CP[b]	Y[b]	Y[b]	CP[b]	CP[b]	Y[b]	UA[b]	UA[b]	UA[b]	UA[b]	Y[b]	N[b]		Y[b]	Y[b]	N[b]
Ertapenem	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]
Meropenem	Y[a, b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]
Nafcillin	CP[b]	Y[b]	CP[b]	CP[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]		CP[b]	CP[b]
Penicillin G	N	CP[b]	N[b]	N[b]	Y[b]	UA[b]	Y[b]	Y[b]	Y[b]	N[b]	Y[b]	Y[b]	Y[b]	Y[b]	N[b]	Y[b]	Y[b]	CP[b]		CP[b]
Piperacillin/tazobactam	N	UA	CP[b]	CP[b]	Y[b]	CP[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	Y[b]	CP[b]	Y[b]	N[b]	CP[b]	CP[b]	

Y The order may be ordered/verified if any reaction other than type I–IV hypersensitivity reaction (HSR). This includes general or non-specific allergy listings. For type I HSRs, a β-lactam with a different side chain CAN be safely administered; however, prescribers should be notified to communicate this information and confirm the order. Avoid use in type II–IV HSRs.

UA "OK Unless Anaphylaxis" Agent may have limited or conflicting data or share a similar (not identical) side chain. Order/verify as long as the reaction is NOT listed as a type I–IV HSR.

N Should not be ordered/verified due to a higher likelihood of cross-reactivity. If ordered, the prescriber should be notified, and a different agent considered.

CP "Call Prescriber" The agent may have limited or conflicting data or share a similar (not identical) side chain. Risk/benefit should be evaluated.

Curtis D Collins, et al. Antibiotic Use in Patients With β-Lactam Allergies and Pneumonia: Impact of an Antibiotic Side Chain–Based Cross-Reactivity Chart Combined With Enhanced Allergy Assessment, Open Forum Infectious Diseases, Volume 9, Issue 1, January 2022.

Technicians

- Which antibiotic can interact with antidepressants and cause serotonin syndrome?
- A) levofloxacin
- B) linezolid
- C) cephalexin

Technicians

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Pharmacist

- Which anti-depressant is more likely to cause serotonin syndrome when combined with linezolid?

- A) citalopram

- B) fluoxetine

- C) bupropion

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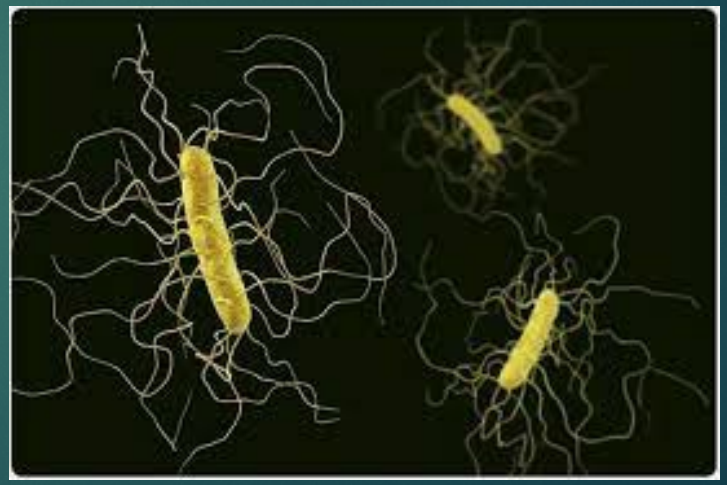
Updates in *Clostridioides difficile* 2021



News-medical.net

The

Facebook.com

- MAJOR threat to global public health
  - 202,600 cases in 2020
  - Exposure to antimicrobials is associated with a 60% increased risk of *C diff*
  - Commonly associated abx:
    - Cephalosporins, clindamycin, carbapenems, TMP-SMX, erythromycin, ß-lactams, and fluroquinolones
- Decrease in hospitalized *C diff* infections in 2019:
  - Increased diagnostic stewardship to reduce inappropriate testing
  - Continued adherence to recommended infection prevention and control measures
  - Continued implementation of inpatient antibiotic stewardship programs

https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf
O'Grady, Keeley, et al. Antimicrobial resistance in *Clostridioides difficile*. European Journal of Clinical Microbiology & Infectious Diseases (2021) 40:2459-24778.

Guideline updates: **Initial** *C diff* episode

- **2017**
  - oral vancomycin 125 mg four times per day x 10 days
  - Fidaxomicin 200 mg twice daily x 10 days
    - Approved in 2011 – first new *C diff* drug in 31 years!!!!
  - Alternative if above not available: metronidazole 500 mg TID x 10 days

- **2021**
  - Fidaxomicin 200 mg twice daily x 10 days
  - Alternative: vancomycin 125 mg four times per day x 10 days
  - Alternative for NONSEVERE if above regimens not available: metronidazole 500 mg TID x 10-14 days

Johnson, Stuart, et al. Clinical Practice Guidelines for C. difficile Infection. CID 2021.

Guideline updates: **Recurrent** *C diff* episode

- **2017**
  - Vancomycin 125 mg 4 times daily x 10 days (if metronidazole – 1st episode)
  - Prolonged taper and pulsed vancomycin (if standard – 1st episode)
    - eg, 125 mg 4x/day x 10-14 days, then 2x/day x 7 days, then once daily x 7 days, then every 2-3 days for 2-8 weeks
  - Fidaxomicin 200 mg twice daily x 10 days (if vanco – 1st episode)
- **2021**
  - Fidaxomicin 200 mg twice daily x 10 days
  - Fidaxomicin 200 mg twice daily x 5 days then every other day x 20 days
  - Alternative: vancomycin tapered and pulsed regimen
  - Alternative: vancomycin 125 mg four times per day x 10 days
  - **adjunctive treatment: Bezlotoxumab

Johnson, Stuart, et al. Clinical Practice Guidelines for C. difficile Infection. CID 2021.

Bezlotoxumab

- FDA approved after 2017 guidelines (briefly mentioned in 2017)
- **Monoclonal antibody targeting toxin B production**
- One-time infusion of 10 mg/kg over 60 minutes
  - Elimination half-life of 18 days = measurable antibody concentrations up to 3 months
- **2021: recommended with recurrent *C diff* within last 6 months**
  - Risk factors for recurrence
    - >/= 65 years
    - Immunocompromised host
    - Severe infection on presentation (wbc >15 or Scr >/= 1.5)
- **FDA warning:**
  - "in patients with a history of congestive heart failure, bezlotoxumab should be reserved for use when the benefits outweighs the risk."

Johnson, Stuart, et al. Clinical Practice Guidelines for C. difficile Infection. CID 2021.

Advantages vs Disadvantages: fidaxomicin vs vancomycin

- Fidaxomicin is only twice daily vs four times daily
- Fidaxomicin has increased sustained response of *C diff* infection 4 weeks after end of therapy compared to standard vanco
- No data supporting fidaxomicin in fulminant *C diff*
- Vancomycin is MUCH MUCH cheaper
  - BUT with the new approved guidelines insurance companies hopefully will start to cover better
  - Patient-assistance programs are available for fidaxomicin

Johnson, Stuart, et al. Clinical Practice Guidelines for C. difficile Infection. CID 2021.

Pharmacist/Technician Case Study:

- F.H. is an 57 year old male admitted with an ESBL E coli urinary tract infection on ertapenem day 5 and has developed diarrhea. He was tested for *C diff* and was positive. Which would be the **preferred** first-line treatment for this first occurrence of *C diff*?
  - A) metronidazole IV
  - B) vancomycin IV
  - C) fidaxomicin oral

Case Study:

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  - B) vancomycin IV
  - **C) fidaxomicin oral**

The NEWEST of antibiotics

Main drivers of resistance:

- Over use
- Inappropriate use in:
  - Humans
  - Agriculture
  - Animals

*antibiotic development is imperative to outpace the ability of pathogens to develop resistance

Chahine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390

New antibiotic approval

- Declining since the 1980s
- High rate of failure during the development phase
- FDA approval process: up to 7 years
- Costly: >$1.29 billion to bring to market
- LOW use of final product
  - Used for acute disease vs chronic disease
- Antimicrobial Stewardship Program restrictions
  - Prefer use of older, less expensive, narrow antibiotics FIRST
  - Often RESTRICTED
- 17 new abx since 2010 and 1 related biologic

Chahine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390

Plazomicin

- Aminoglycoside
- Approved for: **urinary tract infection, complicated (pyelonephritis or urinary tract infection with systemic signs/symptoms)**
- Retains activity against organisms that produce aminoglycoside-modifying enzymes seen in prior aminoglycosides
  - BUT reduced activity against *Pseudomonas* or *Acinetobacter*
- Once-daily dosing
- Reserve for: **carbapenem-resistant Enterobacterales (CRE)**
  - KPC and OXA types

Chahine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390
Lexi-Comp Online Database (2022)

Meropenem/vaborbactam

- Carbapenem/β-lactamase inhibitor
- Approved for: **Urinary tract infection, complicated (pyelonephritis or urinary tract infection with systemic signs/symptoms)**
- TANGO-2 trial comparing meropenem-vaborbactam to best available therapy was stopped early due to a risk-benefit ratio in favor of meropenem-vaborbactam
- Dose: 4 grams IV every 8 hours infused over 3-hours
- Reserve for: infections caused by **carbapenem-resistant Enterobacterales** (**CRE**)
  - KPC

Ishine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390
Lexi-Comp Online Database (2022

ceftaroline

- Cephalosporin: ONLY one active against MRSA
- Approved for: **community acquired pneumonia and skin and soft tissue infections**
- Off label use: bacteremia, endocarditis, meningitis, osteomyelitis, and hospital-acquired pneumonia
- Dose: 600 mg IV every 12 hours

Ishine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390
Lexi-Comp Online Database (2022

cefiderocol

- Novel cephalosporin
  - New mechanism: siderophore-iron complex pathway to penetrate outer membrane of gram negative bacteria
- Approved for: **pneumonia (hospital and ventilator-associated) and complicated urinary tract infections**
- Gram negatives
  - ESBLs, ampCs, CRE (KPC, OXA and MLB), *Pseudomonas, Acinetobacter baumannii, Stenotrophomonas maltophilia*
- Dose: 2 grams IV every 8 hours (could consider every 6 hours w/CrCl >120 mL/min)
- ***warning*** - increased risk of mortality with carbapenem-resistant infections
  - Reserve for: patients with limited or no alternative treatment options in resistant gram negative infections

Hahine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390
Lexi-Comp Online Database (2022

Ceftolozane/tazobactam

- Cephalosporin/β-lactamase inhibitor
- Approved for:
  - **Intra-abdominal (+ metronidazole)**
  - **Pneumonia**
  - **Serious multidrug resistant *Pseudomonas* infections**
  - **Complicated urinary tract infections**
- Dose: 1.5 – 3 grams IV every 8 hours
- Reserve for: infections caused by multidrug resistant *Pseudomonas*

Ishine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390
Lexi-Comp Online Database (2022

Ceftazidime/avibactam

- Cephalosporin/β-lactamase inhibitor
- Approved for:
  - **Intra-abdominal (+ metronidazole)**
  - **Pneumonia**
  - **Complicated urinary tract infections**
- Dose: 2.5 grams IV every 8 hours
- Reserve for: infections caused by multidrug resistant *Pseudomonas*
  - KPC, OXA-48, and other multidrug resistant forms

hahine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390

Delafloxacin

- Fluoroquinolone
  - MRSA, streptococci, ESBLs, and Pseudomonas
- Approved for:
  - **Pneumonia**
  - **Skin and soft tissue infections**
- Dose:
  - Oral: 450 mg every 12 hours
  - IV: 300 mg every 12 hours
- Many labs do not have susceptibility information
- Not associated with photosensitivity and clinically relevant QTc prolongation

hahine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390

Dalbavancin and oritavancin

- LONG-ACTING lipoglycopeptides (MRSA agents)
- **Dalbavancin**
  - Approved for: **skin and soft tissue infections**
  - Dose: 1.5 g as single dose OR 1 g followed by 500 mg in one week
- **Oritavancin**
  - Approved for: **skin and soft tissue infections**
  - Dose: 1.2 g as a single dose
  - *prolongs certain coagulation tests; contraindicated use with heparin 5 days after administration; caution with used with warfarin as can artificially prolong INR
- Off-label use: endocarditis, osteomyelitis, and septic arthritis

hahine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390

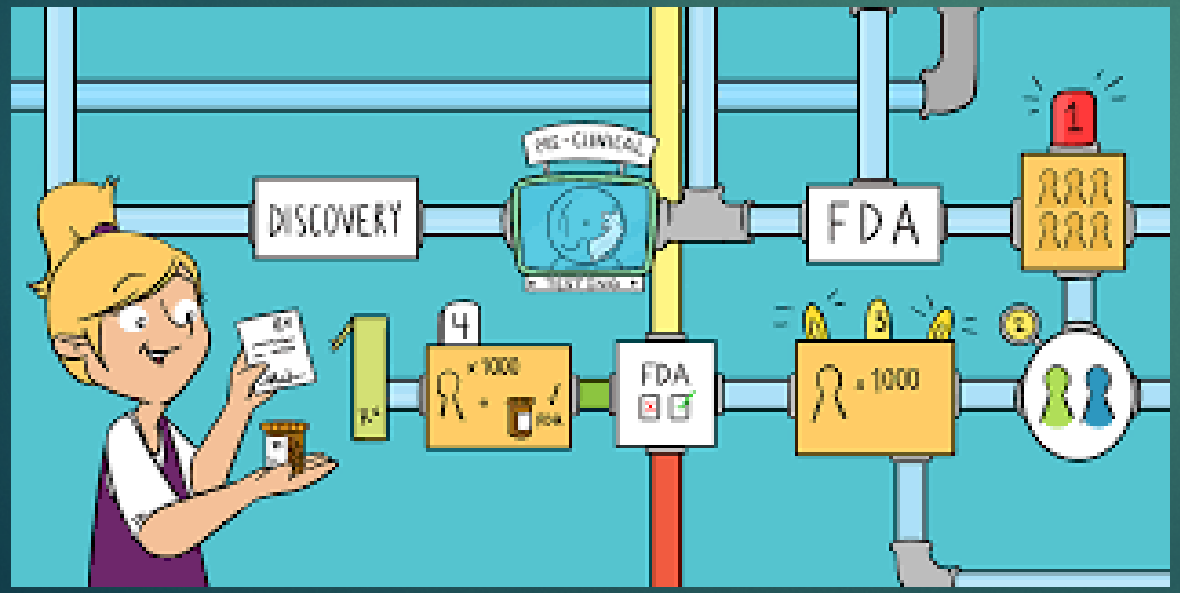
Eravacycline and **omadacycline**

- Broad-spectrum tetracyclines
  - MRSA, VRE, CRE, ESBL, *Acinetobacter*, *Stenotrophomonas*, anaerobes (NO *Pseudomonas*)
- **eravacycline**
  - Approved for: **intra-abdominal infections**
  - Dose: 1 mg/kg IV every 12 hours
- **omadacycline**
  - Approved for: **plague, community-acquired pneumonia, skin and soft tissue infection**
  - Dose:
    - Pneumonia – IV 100 mg BID x 1 day then 100 mg daily; ORAL 300 mg BID x 1 day then 300 mg once daily
    - Skin and soft tissue – IV 100 mg BID x 1 days then 100 mg daily; ORAL 450 mg daily on days 1 & 2 then 300 mg daily

hahine EB, Dougherty JA, Thornby K-A, Guirguis EH. Antibiotic Approvals in the Last Decade: Are We Keeping Up With Resistance? Annals of Pharmacotherapy. 2022;56(4):441-462. doi:10.1177/10600280211031390

In the pipeline

- **Tebipenem**: oral carbapenem for urinary tract infections
  - Spring 2022 – the FDA ultimately concluded that Spero's Phase 3 cUTI study of tebipenem HBr (ADAPT-PO) was insufficient to support approval and that additional clinical study would be required



https://kids.frontiersin.org/articles/10.3389/frym.2020.532921

hhttps://sperotherapeutics.com/pipeline/tebipenem-hbr-oral-gram-negative-program/

Go to references:

- **Idsociety.org (Infectious Disease Society of America)**
  - ALL the current guidelines for treatment
- **The Sanford Guide to Antimicrobial Therapy**
  - Phone app or paper versions available
- **John Hopkins ABX Guide**
  - Phone app or paper versions available
- **Antibiotics Simplified (Jason C. Gallagher and Conon MacDougall)**
  - 5th edition just released (Amazon, Barnes & Noble, etc)
- **www.idstewardship.com**
  - Free information as well as more with a membership

https://apastyle.apa.org/images/new-reference-examples_tcm11-270270.jpg

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Santee.sd.net

Beth Loecker:
beth.loecker@sanfordhealth.org