OUTSMARTING SUPERBUGS: A NURSE'S GUIDE TO DRUG RESISTANCE

Emily Herstine, PharmD, BCPS, BCIDP
ANW Clinical Pharmacy Specialist-Infectious Diseases

April 17, 2024

Antimicrobial Stewardship

Allina Health

1

Objectives

Upon completion of this lecture, participants should be able to:

1. Describe impact of drug resistance and opportunities for prevention

2

Overview

Resistance & Impact

Candida auris & Carbapenem-resistant Enterobacterales

Prevention & Action Opportunities

3

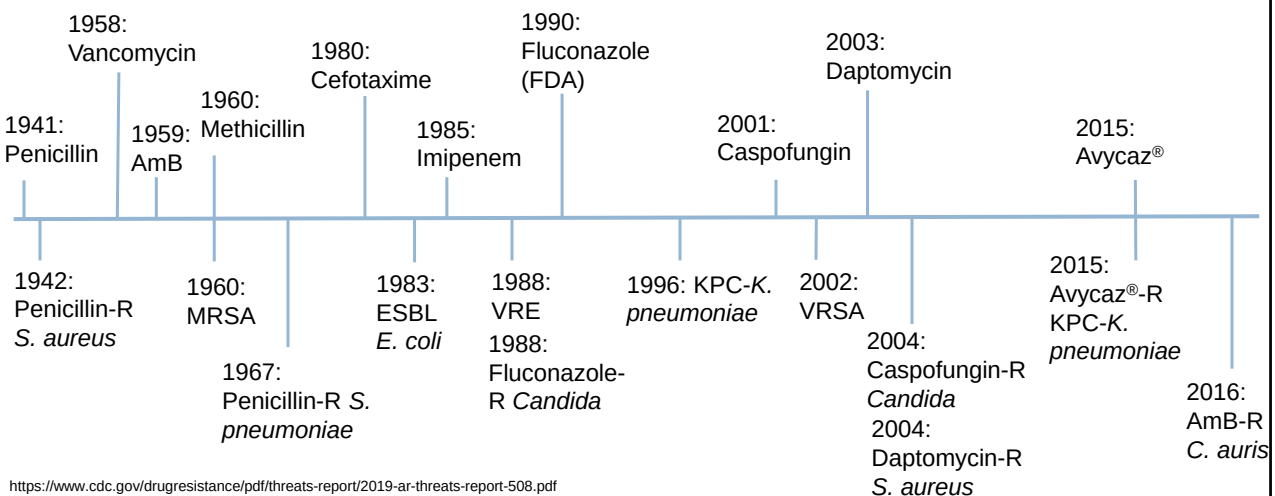
Abbreviations

- AmB: amphotericin B
- AMR: antimicrobial resistance
- AST: antimicrobial susceptibility testing
- BLI: beta-lactamase inhibitor
- CLSI: clinical & laboratory standards institute
- CRAB: carbapenem resistant *Acinetobacter baumanii*
- CRE: carbapenem resistant Enterobacterales
- CRO: carbapenem resistant organism
- CP-CRO: carbapenemase producing CRO
- Enterobacterales: enteric Gram-negative bacilli (formerly named Enterobacteriaceae)
- ESBL: extended spectrum beta lactamase
- FDA: Food and Drug Administration
- IMP: imipenem-hydrolyzing metallo-β-lactamases
- KPC: *Klebsiella pneumoniae* carbapenemase
- MDR: multidrug-resistant
- MRSA: methicillin resistant *Staphylococcus aureus*
- NDM: New Delhi metallo-β-lactamases
- OXA-48-like: oxacillinases
- VIM: verona integron-encoded metallo-β-lactamases
- VRE: vancomycin resistant *Enterococcus*
- VRSA: vancomycin resistant *Staphylococcus aureus*

4

5

Resistance Over Time



https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

6

Impact of Antimicrobial Resistance

Global deaths due to antimicrobial resistance (AMR) will outpace cancer by 2050 if we do not act

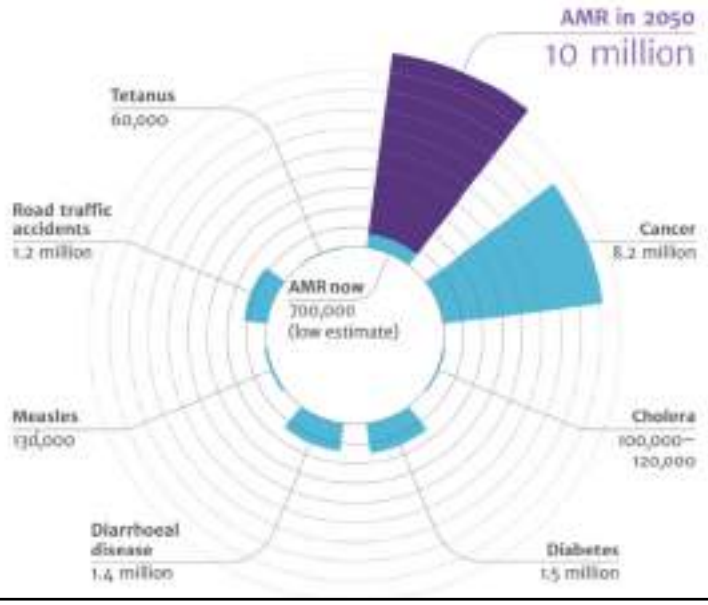


Figure available via license: Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International 'Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. 2014.'

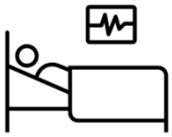
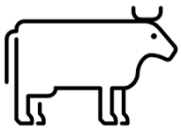
7

Antimicrobial Resistance Spreads Easily

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

8

One Health

Minnesota One Health Antibiotic Stewardship Collaborative

9

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

10

Development of Antimicrobial Resistance

Most important factors

- **Unnecessary** antimicrobial use (prescribed when **not** needed)
- **Excessive** antimicrobial use (course is **too long**)
- Unnecessary use of **broad-spectrum** antimicrobials (antimicrobials are too broad)

30-50% of antibiotics prescribed in U.S. acute care hospitals and in outpatient setting are **unnecessary** or **inappropriate**

CDC and National Quality Partners Playbook™: Antibiotic Stewardship in Acute Care, July 2016
https://www.cdc.gov/antibiotic-use/community/programs-measurement/measuring-antibiotic-prescribing.html#f7 Accessed 8/15/2019

11

COVID-19 Impact on AMR

- 2022 Special Report from CDC highlighted multiple challenges
  - Detection & reporting of AMR data slowed significantly

  - Observed antibiotic use increased
    - From 3/2020 to 10/2020, almost 80% of patients hospitalized with COVID-19 received an antibiotic

2022 SPECIAL REPORT: COVID-19 U.S. Impact on Antimicrobial Resistance (cdc.gov)

12

CDC Antibiotic Resistant Threats in the US

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- ESBL-producing Enterobacterales
- Vancomycin-resistant *Enterococci* (VRE)
- MDR *Pseudomonas aeruginosa*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Samonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *S. aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis (TB)

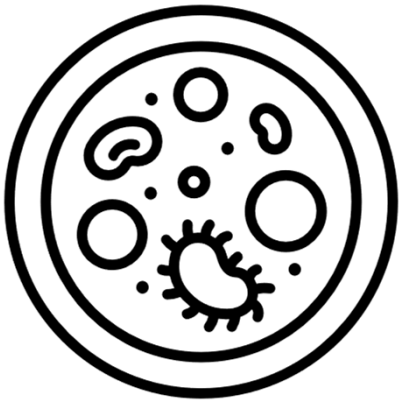
Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridiodes difficile (C. difficile)*
- Carbapenem-resistant Enterobacterales
- Drug-resistant *Neisseria gonorrhoeae*

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

13

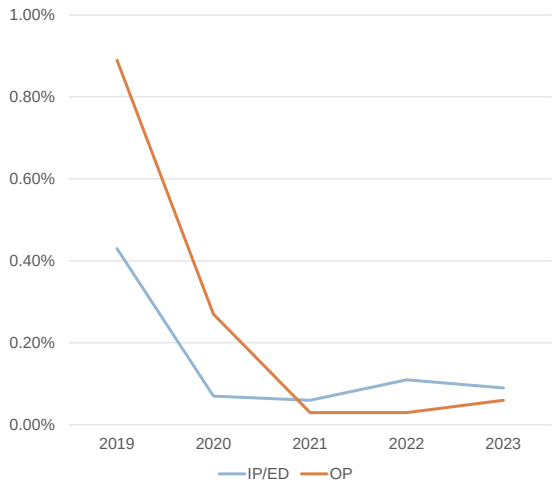
Allina MDRO Data



- 2020 was somewhat of an anomaly year
- New susceptibility card in 2020
  - Imipenem to meropenem

14

Carbapenem-R Enterobacterales at Allina

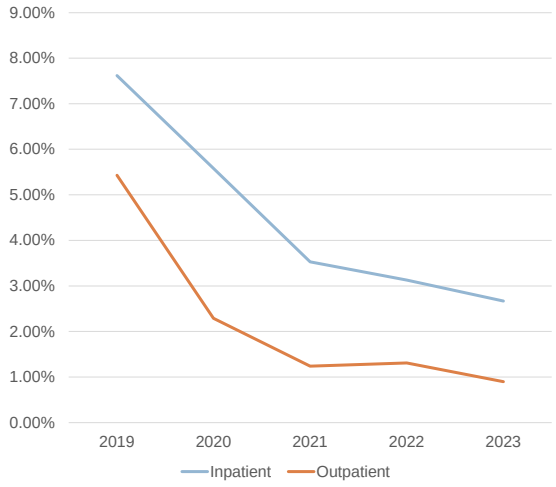


Year	Inpatient (n)	Outpatient (n)
2019	42*	122*
2020	6	30
2021	7	4
2022	12	5
2023	11	9

*Imipenem carries some intrinsic resistance

15

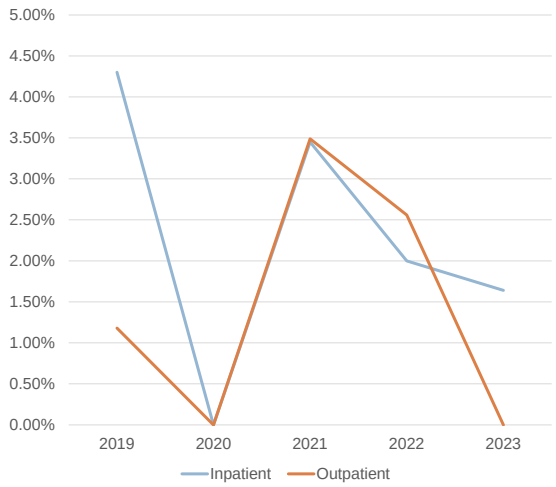
Carbapenem-R *Pseudomonas aeruginosa*



Year	Inpatient (n)	Outpatient (n)
2019	67	30
2020	44	10
2021	35	8
2022	35	8
2023	32	6

16

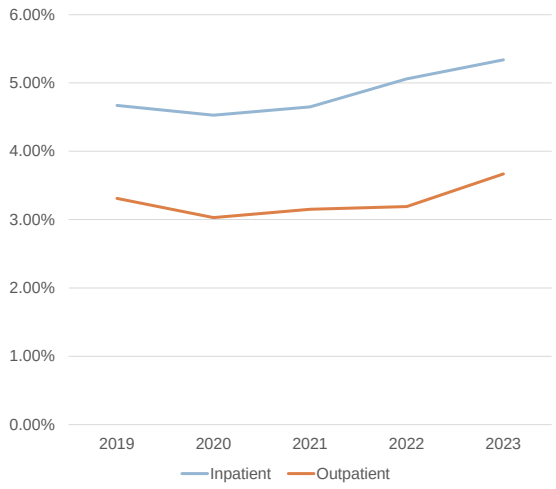
Carbapenem-R *Acinetobacter*



Year	Inpatient (n)	Outpatient (n)
2019	4	1
2020	0	0
2021	3	3
2022	2	1
2023	2	0

17

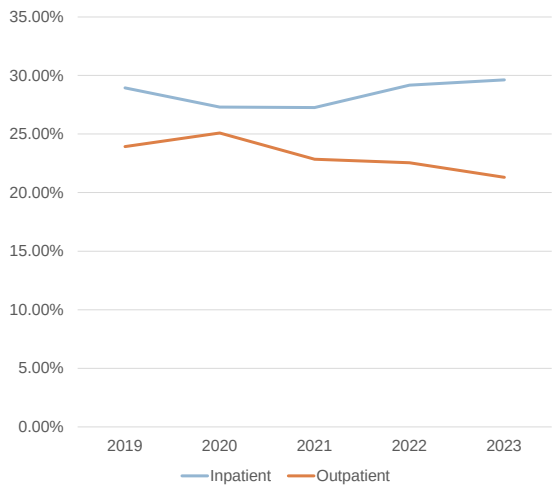
ESBL positive *E. coli, Klebsiella & P. mirabilis*



Year	Inpatient (n)	Outpatient (n)
2019	402	416
2020	364	311
2021	441	430
2022	492	439
2023	560	512

18

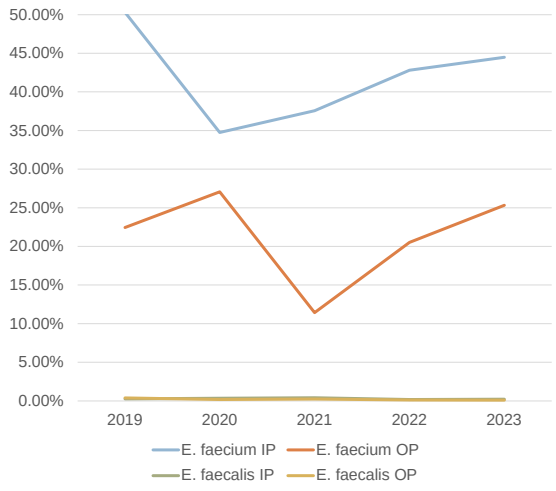
Methicillin Resistant *Staphylococcus aureus*



Year	Inpatient (n)	Outpatient (n)
2019	739	534
2020	650	417
2021	718	426
2022	817	412
2023	856	437

19

Vancomycin Resistant *Enterococcus*



Year	E. faecium IP (n)	OP (n)	E. faecalis IP (n)	OP (n)
2019	82	11	7	5
2020	57	13	5	2
2021	83	8	8	4
2022	95	16	4	2
2023	125	19	5	2

20

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

21

Carbapenem Resistant Enterobacterales

- Member of the Enterobacterales order resistant to at least one carbapenem or producing a carbapenemase enzyme
- CRE organisms are often resistant to multiple classes of antibiotics
- 35-59% of CRE in the United States are carbapenemase-producing isolates
  - KPCs are the most common (not limited to *K. pneumoniae)*
  - NDMs, VIMs, IMPs, & OXA-48-like also observed
- Main risk factors in US are exposure to **healthcare** & exposure to **antibiotics**

https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed: 3/28/2024
Clinicians: Information about CRE | HAI | CDC. Accessed: 3/28/2024

22

CRE Treatment

- Options **highly dependent** on mechanism of resistance & site of infection
- Novel β-lactam agents are often preferred treatment
  - Ceftazidime-avibactam (Avycaz®)
  - Meropenem-vaborbactam (Vabomere®)
  - Imipenem-cilastatin-relebactam (Recarbrio®)
  - Cefiderocol (Fetroja®)
- AST results often need to be requested to be performed
- Antimicrobial stewardship is **critical** to preserve susceptibility of novel agents

23

IDSA 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

Published by IDSA on 6/7/2023. Document is current as of 12/01/22. 7/1/2023

A Focus on Extended-spectrum β-lactamase-Producing Enterobacterales, AmpC β-Lactamase-Producing Enterobacterales, Carbapenem-Resistant Enterobacterales, *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance, Carbapenem-Resistant Acinetobacter *baumannii*, and *Stenotrophomonas maltophilia*

24

Carbapenemase Resistance

Genotype	Mechanism	Resistance to	Alternative β-lactams
KPC	Penicillinase, cephalosporinase, carbapenemase (class A β-lactamase)	Penicillins Penicillin-BLI combinations Cephalosporins Carbapenems Aztreonam	Ceftazidime-avibactam Meropenem-vaborbactam Imipenem-cilastatin-relebactam Cefiderocol
OXA-48 OXA-48-like	Penicillinase, carbapenemase (class D β-lactamase)	Penicillins Penicillin-BLI combinations Carbapenems Aztreonam	Ceftazidime-avibactam Cefiderocol
IMP, VIM, NDM	Penicillinase, cephalosporinase, carbapenemase (class D β-lactamase)	Penicillins Penicillin-BLI combinations Cephalosporins Carbapenems	Aztreonam **PLUS** ceftazidime-avibactam Cefiderocol

https://webedition.sanfordguide.com/en/drug-information/antibacterial-agents/antibacterial-drug-resistance-genotypes. Accessed 3/28/24

25

CRE Treatment-Role of Polymyxins?

IDSA suggests avoiding polymyxin B and colistin for treatment

- CLSI eliminated susceptible category → concerns around effectiveness & accuracy of AST

Increased mortality ✖

Excess nephrotoxicity

2023 systematic review & meta-analysis comparing ceftazidime-avibactam vs polymyxins in treating CRE infections (n=833 patients)

- ⇩ 30-day mortality (p<0.00001)
- ⇧ clinical cure rate (p<0.00001)
- ⇧ microbial clearance rate (p<0.00001)

Chen, J., Hu, Q., Zhou, P. *et al.* Ceftazidime–avibactam versus polymyxins in treating patients with carbapenem-resistant Enterobacteriaceae infections: a systematic review and meta-analysis. *Infection* **52**, 19–28 (2024). https://doi.org/10.1007/s15010-023-02108-6

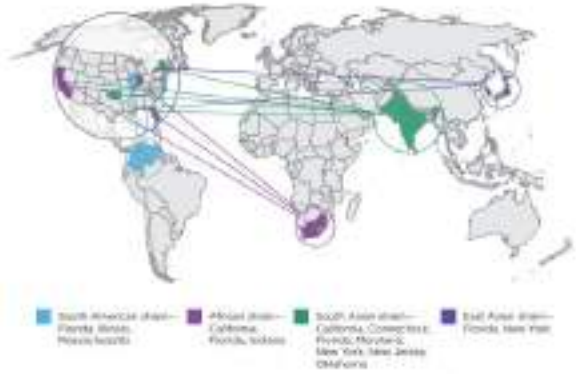
26

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

27

Candida auris

- *C. auris* first identified in 2009 in Japan
  - Retrospective review of *Candida* strain collections show earliest known strain in 1996 in South Korea
- Mostly affects patients with severe underlying medical condition requiring complex medical care
- Estimated crude mortality rate of 34%
- Colonization can persist for prolonged periods of time



https://www.cdc.gov/fungal/diseases/candidiasis/candida-auris-qanda.html. Accessed 7/31/17
https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Benedict K, Forsberg K, Gold J, et al. Candida auris–Associated Hospitalizations, United States, 2017–2022. *Emerging Infectious Diseases*. 2023;29(7):1485-1487. doi:10.3201/eid2907.230540.

28

Why is *Candida auris* a problem?

- Causes serious infections
- Often multidrug resistant
- Becoming more common
- Difficult to identify
- Can spread in hospitals and nursing homes

29

Candida auris in the United States — 2017

https://www.cdc.gov/fungal/diseases/candidiasis/candida-auris.html. Accessed 7/31/17

30

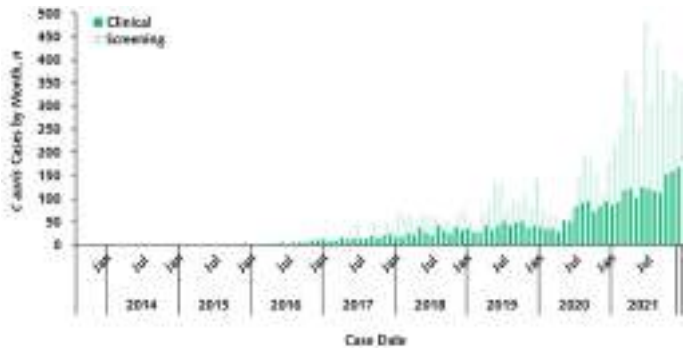
Candida auris in the United States — 2022

https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html. Accessed 7/31/17

31

Candida auris in the United States

- Case counts reported to the CDC



- Schaefer et al published March 2024: academic tertiary hospital reported a significant increase in identification from 2.6 cases per 10,000 admissions in 2019 to 7.8 in 2022

Ann Intern Med. 2023; 176(4):489-495. doi:10.7326/M22-3469

32

Antifungal Susceptibility for *Candida auris*

All *C. auris* isolates should undergo AST per CLSI

Currently no established *C. auris*-specific susceptibility breakpoints

- Defined based on established closely related *Candida* species and expert opinion

Correlation between breakpoints and clinical outcomes is not known

https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html. Accessed 3/28/24

33

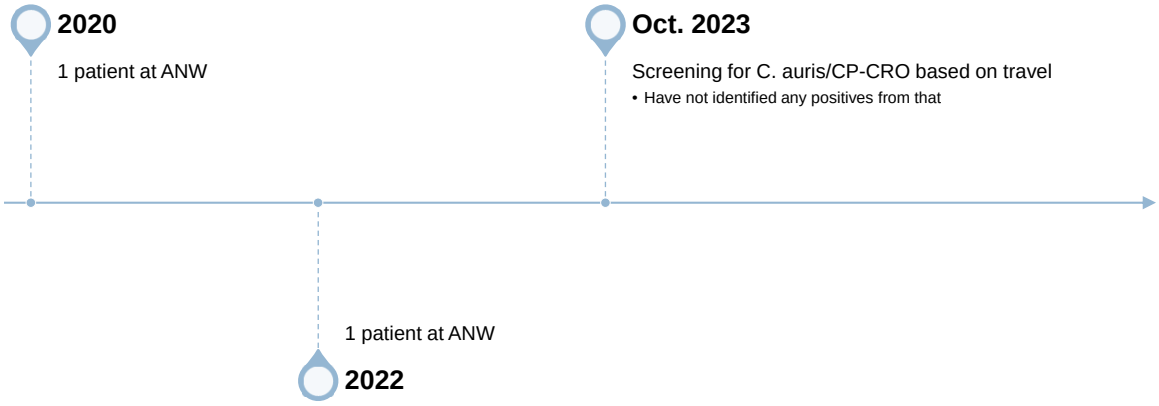
Candida auris Treatment

- Consultation with an infectious disease specialist is highly recommended
- Recommend echinocandin as initial therapy
  - Consider switch to liposomal amphotericin B if clinically unresponsive to echinocandin or persistent fungemia >5 days
- Appears to develop resistance quickly & may need repeat AST
- Data lacking on most appropriate therapy for pan-resistant strains
  - May consider investigational drugs under expanded access programs

https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html. Accessed 3/28/24

34

Candida auris at Allina Health



35

CDC Core Actions to Prevent Resistance

Infection Prevention & Control

Tracking & Data

Antibiotic Use & Access

Vaccines, Therapeutics & Diagnostics

Environment & Sanitation

36

Allina Travel Screening

- Updated system-wide in October 2023
- If “yes” will prompt screening for C. auris/CP-CRO

37

Antibiotic Development

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

38

What is Antimicrobial Stewardship?

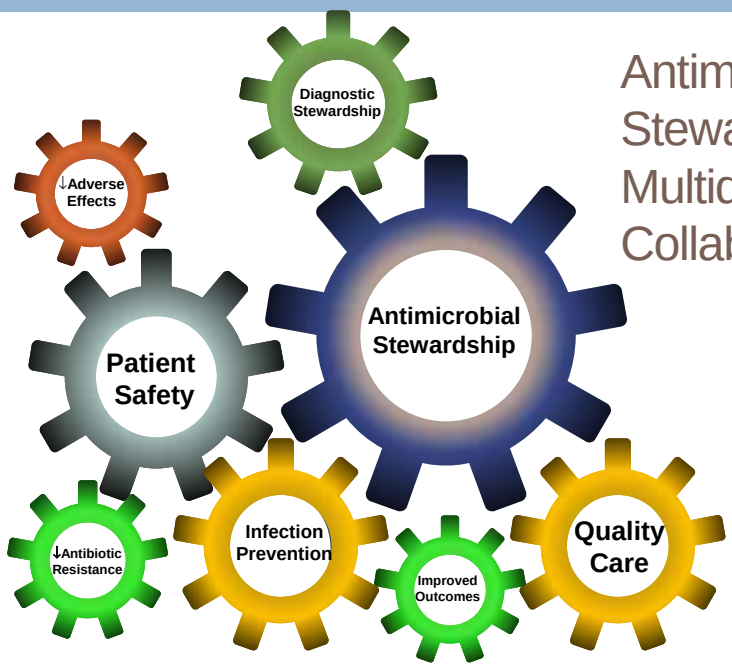
*Antimicrobial stewardship refers to **coordinated** interventions designed to **improve and measure** the **appropriate use** of antimicrobials by promoting the selection of the **optimal** antimicrobial drug regimen, dose, duration of therapy, and route of administration.*

Antimicrobial stewards seek to…

- ✓ Achieve **optimal** clinical **outcomes** related to antimicrobial use
- ✓ **Minimize toxicity** and other adverse events
- ✓ **Reduce the costs** of health care for infections
- ✓ **Limit** the selection for antimicrobial **resistance**

39

Antimicrobial Stewardship is a Multidisciplinary Collaboration



40

41

Allina Antimicrobial Stewardship Program Committee (AASPC)

41

CDC Core Elements of Antimicrobial Stewardship: Nursing Engagement

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

There is **growing recognition** of the importance of **engaging nurses** in hospital stewardship efforts. Nurses can play an especially important role in:

- Optimizing testing, or **diagnostic stewardship**. For example, nurses can inform decisions about whether or not a patient has symptoms that might justify a urine culture
- Assuring that **cultures** are performed correctly before starting antibiotics
- **Prompting discussions** of antibiotic treatment, indication, and duration
- Improving the documentation and evaluation of **penicillin allergies**

https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf

42

Antimicrobial Stewardship

Penicillin Allergies

Asymptomatic Bacteriuria

43

44

Penicillin allergies are prevalent

More than 10% of the US population reports a penicillin allergy

95% of patients with reported penicillin allergy can tolerate penicillins when tested

44

45

Penicillin allergies cause harm

- ↑ Antibiotic resistance
- ↑ *C. difficile*
- ↑ Mortality
- ↑ Surgical site infections
- More

45

Inaccurate Penicillin Allergy Labels Cause Harm

Patients **inappropriately** labeled with a penicillin allergy label receive **second line**, **inferior** antibiotics **unnecessarily**.

Paradox

- Penicillin allergy labels **intend to**:
  - Improve patient safety
  - Minimize harm
  - Reduce adverse events

BUT

- Penicillin allergy labels are **recognized to**:
  - Compromise patient outcomes
  - Promote antibiotic resistance
  - Increase adverse events

Common reasons for incorrect label include **family history** and **intolerances** (isolated headaches, nausea, vomiting, diarrhea, dizziness or fatigue)

46

Penicillin Allergy Labels

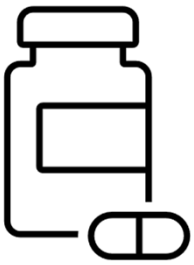
- Do **not** document **family history** of penicillin allergy as allergy.
- Do **not** document **intolerances** (e.g. nausea, diarrhea, headache) as penicillin allergy.
- Document antibiotic allergies accurately:
  - What antibiotic caused the reaction?
  - What was the reaction?
  - How soon did the reaction happen after the antibiotic dosing?

Penicillin allergy labels are **easily entered** in the EMR but are **hard to remove**.

47

Antimicrobial Stewardship

Penicillin Allergies



Asymptomatic Bacteriuria

48

Asymptomatic Bacteriuria (ASB)

- Urinalysis is a non-specific test that cannot be used alone to diagnose a UTI
- Urine cultures should only be ordered if patients have urinary symptoms
  - Careful observation is recommended in older patients with functional and/or cognitive impairment with delirium (acute mental status change, confusion) and without symptoms or other systemic signs of infection (e.g., fever or hemodynamic instability)
- Treating ASB with antibiotics does NOT benefit patients outside of those undergoing an invasive urological procedure and pregnant patients
- Unnecessary treatment increases the risk for antimicrobial resistance, *C. difficile* infections, UTI recurrence in some populations, and cost

- **Unnecessary urine cultures** → **Unnecessary antibiotics for ASB**

49

Asymptomatic Bacteriuria (ASB)

Urine **Color**

- Isolated urine color changes do **not** correlate well with UTI and should not prompt urine culture in absence of other signs and symptoms of infection

Urine **Odor**

- Urine odor (including foul smell) is **not** an accurate predictor of UTIs

- Reasons for odorous urine:
  - Uncontrolled diabetes
  - Diet (e.g., asparagus)
  - Vitamins
  - Concentrated urine (dehydration)

https://www.hopkinsmedicine.org/-/media/antimicrobial-stewardship/urinary-tract-infection-101-nurses-slide-deck.pdf

50

Conclusions

Drug-resistance is an ongoing threat in the US and globally

Collaborative efforts are needed to address drug-resistance

51

Assessment Question

- Antimicrobial stewardship can help prevent drug-resistance?

True or False?

52

References

1. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin “allergy” in hospitalized patients: A cohort study. J Allergy Clin Immunol. 2014; 133(3): 790-796
2. Blumenthal K, Lu N, Zhang Y, et al. Recorded Penicillin Allergy and Risk of Mortality: a Population-Based Matched Cohort Study. J Gen Intern Med. 2019;34(9):1685-1687.
3. Blumenthal K, Ryan E, Li Y, et al. The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk. Clin Infect Dis. 2018;66(3):329-336.
4. Lindsay E Nicolle and others, Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America, *Clinical Infectious Diseases*, Volume 68, Issue 10, 15 May 2019, Pages e83–e110, https://doi.org/10.1093/cid/ciy1121
5. Schulz, L., Hoffman, R. J., Pothof, J., & Fox, B. (2016). Top ten myths regarding the diagnosis and treatment of urinary tract infections. *The Journal of emergency medicine*, *51*(1), 25-30.
6. Johnson MD, Davis AP, Dyer AP, Jones TM, Spires SS, Ashley ED. Top Myths of Diagnosis and Management of Infectious Diseases in Hospital Medicine. *Am J Med*. 2022;135(7):828-835. doi:10.1016/j.amjmed.2022.03.019
7. Cai T, Nesi G, Mazzoli S, et al. Asymptomatic bacteriuria treatment is associated with a higher prevalence of antibiotic resistant strains in women with urinary tract infections. *Clin Infect Dis*. 2015;61(11):1655-1661. doi:10.1093/cid/civ696
8. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America **2023**; Version 3.0. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed 28 March 2024.
9. https://webedition.sanfordguide.com/en/drug-information/antibacterial-agents/antibacterial-drug-resistance-genotypes. Accessed 3/28/24
10. CDC. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2022. https://www.cdc.gov/drugresistance/covid19.html
11. CDC. Antibiotic Resistance Threats in the United States, 2019. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2019.
12. Chen, J., Hu, Q., Zhou, P. *et al.* Ceftazidime–avibactam versus polymyxins in treating patients with carbapenem-resistant Enterobacteriaceae infections: a systematic review and meta-analysis. *Infection* **52**, 19–28 (2024). https://doi.org/10.1007/s15010-023-02108-6
13. Clinicians: Information about CRE | HAI | CDC. Accessed: 3/28/2024
14. Meghan Lyman, Kaitlin Forsberg, D. Joseph Sexton, et al. Worsening Spread of *Candida auris* in the United States, 2019 to 2021. Ann Intern Med.2023;176:489-495. [Epub 21 March 2023]. doi:10.7326/M22-3469
15. https://www.cdc.gov/fungal/diseases/candidiasis/candida-auris-qanda.html. Accessed 7/31/17
16. Benedict K, Forsberg K, Gold J, et al. Candida auris–Associated Hospitalizations, United States, 2017–2022. *Emerging Infectious Diseases*. 2023;29(7):1485-1487. doi:10.3201/eid2907.230540.
17. Sarah Schaefer, Gopi Patel, Emily Walits, Kalani Thaler, Impact of the COVID-19 Pandemic on *Candida auris* Infections: A Retrospective Analysis in an Academic Medical Center in New York City, *Open Forum Infectious Diseases*, 2024;, ofae148, https://doi.org/10.1093/ofid/ofae148

53

Questions?

54

Contact Information

- Emily Herstine, PharmD, BCPS, BCIDP
  - ANW Clinical Pharmacy Specialist-Infectious Diseases
- Emily.Herstine@Allina.com

Antimicrobial Stewardship

Allina Health

55