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Antimicrobial Stewardship Challenges in Immunocompromised Patients

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January 2025

Objective

Review the importance and challenges of local, institutional, and **intrahospital** epidemiology in driving antibiotic stewardship (ABS) in immunosuppressed (IMS) hematologic malignancy patients

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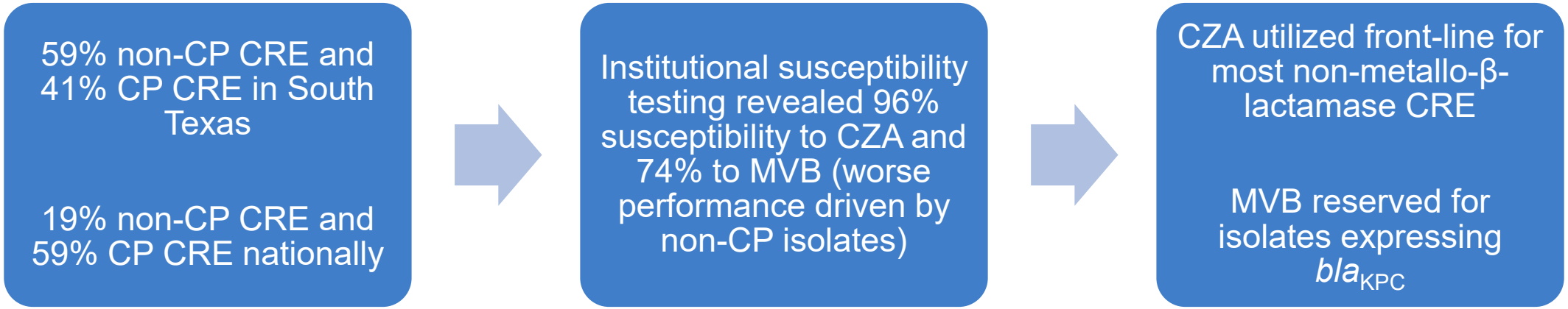
ABS in Hematologic Malignancy Patients

Importance of local + institutional epidemiology in IMS patients

- **Local and institutional epidemiology can inform initial treatment and formulary choices**



- **Non-CP CRE emerge from ESBL-positive Enterobacterales through β-lactamase amplifications and porin changes, likely driven by antibiotic pressure**

- **So why not limit carbapenem and extended-spectrum cephalosporin exposure?**

Black CA, et al. *Front Microbiol*. 2021;11:623574.
van Duin D, et al. *Lancet Infect Dis*. 2020;20(6):731-741.
Shropshire WC, et al. *J Antimicrob Chemother*. 2020;76(2):385-395.
Shropshire WC, et al. *mSystems*. 7(5):e00476-22.
Shropshire WC, et al. *J Infect Dis.* 2024 Nov 27:jiae587.

CRE: carbapenem-resistant Enterobacterales
CP: carbapenemase producing
CZA: ceftazidime-avibactam
ESBL: extended-spectrum β-lactamase
MVB: meropenem-vaborbactam


ANTIBIOTIC STEWARDSHIP
REDUCING FURTHER ANTIMICROBIAL RESISTANCE
HEMATOLOGIC PATIENTS WITH 50% ESBL RATE
ANTIBIOTIC STEWARDSHIP
REDUCING FURTHER ANTIMICROBIAL RESISTANCE
imgflip.com

Intrahospital epidemiology can paint a stark reality

	Hospital-wide % susceptible					
	2023			2024		
	EC (n=1950)	KP (n=878)	SE (n=458)	EC (n=1920)	KP (n=959)	SE (n=402)
Ceftriaxone	**80%**	**83%**	-	**75%**	**82%**	-
Cefepime	**90%**	**90%**	-	**83%**	**87%**	-
ESBL positive	**17%**	**15%**	-	**22%**	**16%**	-
Ertapenem	99%	98%	-	98%	98%	-
Meropenem	99%	97%	-	99%	98%	-
Linezolid	-	-	89%	-	-	92%
	Leukemia and Stem Cell Transplant % susceptible					
	n=187	n=58	n=122	n=175	n=61	n=85
Ceftriaxone	**57%**	**46%**	-	**48%**	**50%**	-
Cefepime	**70%**	**62%**	-	**60%**	**65%**	-
ESBL positive	**40%**	**50%**	-	**51%**	**41%**	-
Ertapenem	98%	91%	-	91%	80%	-
Meropenem	98%	87%	-	93%	85%	-
Linezolid	-	-	67%	-	-	68%

EC: *Escherichia coli*
KP: *Klebsiella pneumoniae*
SE: *Staphylococcus epidermidis*

Initial therapy stewardship in setting of high baseline resistance?

- **Traditional frameworks like preauthorization may not be optimal**

- **Restrictions based on usage criteria could be considered as an alternative**
  - Focusing on judicious use of newer agents (e.g., novel β-lactam/β-lactamase inhibitors) for heme service lines
  - Explore moderation of extended-spectrum cephalosporins and carbapenems in lower-risk non-heme service lines

Ceftazidime/Avibactam	Criteria restricted	• Use is restricted to patients with a positive culture for or documented history of carbapenem-resistant Enterobacterales (CRE)
Ceftolozane/Tazobactam	Criteria restricted	• Use is restricted to positive culture for or history of *Pseudomonas aeruginosa* in a patient where none of the following are acceptable options due to non-susceptibility and/or intolerance: ceFEPime, CefTAZidime, imipenem or meropenem, piperacillin-tazobactam

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Order Questions

Question	Answer	Comment
Positive culture or documented history of Pseudomonas aeruginosa infection?	Yes	
Provide culture source and date collected (if applicable)	1/12/25 Trachael aspirate	
Please select all drugs the patient has demonstrated non-susceptibility and/or intolerance	CeFEPime	
	CefTAZidime	
	Imipenem or Meropenem	
	Piperacillin-tazobactam	

Initial therapy stewardship in setting of high baseline resistance?

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- **Accompanied by prospective audit and feedback for all restricted agents**

Restricted Medications	Number of orders reviewed						
	FY2018	FY2019	FY2020	FY2021	FY2022	FY2023	FY2024
Overall reviews	103	209	225	208	219	197	202

- **In-person rounding with multi-disciplinary ID team**

Ensure coverage of MDROs in the highest acuity infections

- **De-escalation remains an important stewardship component for IMS patients**
- **However, clinically appropriate escalation should not be overlooked**
- **FY2024**
  - 67% of antimicrobial-related stewardship interventions were escalations for bug/drug mismatch

Reviewed	Last Reviewed By	Review Comment	Result Time	Patient	MRN	Unit and Room	Age	Source	Specimen Type	Collected	Service	Last Lab Results	Comment Results
✓	Jovan Borjan, RPH	12/16 JB - nAML, recent 7/5/24 ESBL E coli BSI, now MUD SCT 12/9/24 D+7 awaiting engraftment and new E coli BSI (CVC +, periph taken later so far NGTD), pt afeb and HDS on MEM, f/u sensi; 12/17 JB - still awaiting engraftment, E coli ESBL again, doing well on MEM, no AST f/u at this time;	02:21:51 PM	[redacted]				Central Venous Catheter	Blood	12/15/2024 1051	Stem Cell Transplant and Cellular Therapy	BLOOD CULTURE: Escherichia coli	

MDRO: multidrug-resistant organism

Antimicrobial continuation, discontinuation, and de-escalation

Antimicrobial time-outs (ATO) used as formal review of patient's antibiotic after initiation

EPIC did not feature the needed functionality at the time

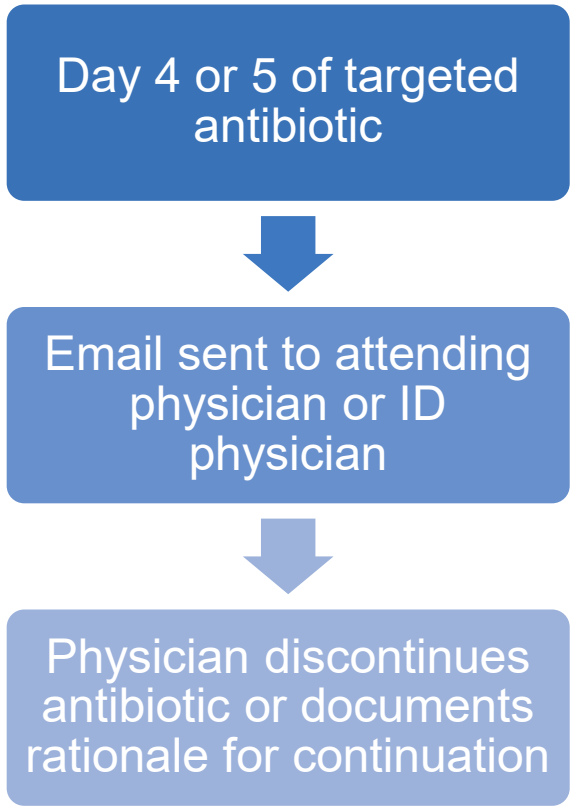
Worked with internal application analysts to develop a customized alerting system

ABX Antimicrobial Time-out System

ABX

- Automated email-based time-out system
  - Email directed to listed attending EPIC at ~8:30 am
- Providers review need for continued use of targeted antimicrobials after 4-5 days of therapy
- Department and individual provider compliance can be reported to service line leadership and quality officers

Workflow



Targeted antimicrobials

- Ceftazidime-avibactam
- Ceftolozane-tazobactam
- Cefiderocol
- Daptomycin
- Eravacycline
- Sulbactam--durlobactam
- Linezolid
- Imipenem
- Meropenem
- Meropenem/vaborbactam
- Tigecycline
- Vancomycin (IV/PO)
- Piperacillin-tazobactam (**only Hospital Medicine**)
- Cefepime (**only Hospital Medicine**)
- Maribavir

Targeted services

- Leukemia
- Stem cell transplant
- Lymphoma/Myeloma
- Hospital Medicine
- All ID consult services

ABX Email

ABX: Day 4 Targeted Antimicrobial Notification

AN AntimicrobialNotification@mdanderson.org
To [redacted] Borjan,Jovan; Vuong,Nancy N; Castro,Gilbert D; **PharmacyDataMgmtAppDev**

Reply | Reply All | Forward

Wed 3/13/2024 9:01 AM

[redacted]

The Antimicrobial Stewardship Team has identified the following patient(s) who are receiving a targeted antimicrobial as per The Antimicrobial Stewardship Program Policy (CLN0594) for at least 4 days of whom you are designated the Inpatient Attending Physician. This memo is being sent to you as a reminder to assess the indication for the following antimicrobial(s):

MRN	Patient Name	Antibiotic	Tracking Database
[redacted]	[redacted]	*ceFEPime (MAXIPIME)*	*20240313279740895557*
[redacted]	[redacted]	*piperacillin-tazobactam (ZOSYN)*	*20240313281564811744*

To ensure compliance with the policy, an overview of the procedures that need to be followed for targeted antimicrobials:

- **If the antimicrobials are to be continued**, you, or a designee*, are required to click on the hyperlink above(number listed under "tracking database") to document the indication.
- **If you discontinue antibiotic therapy on the day of the alert**, you do NOT need to document an indication.
- **Continuing these antibiotics beyond day 4 without the appropriate documentation is considered noncompliance with this institutional policy and will be tracked by your departmental quality officer.**

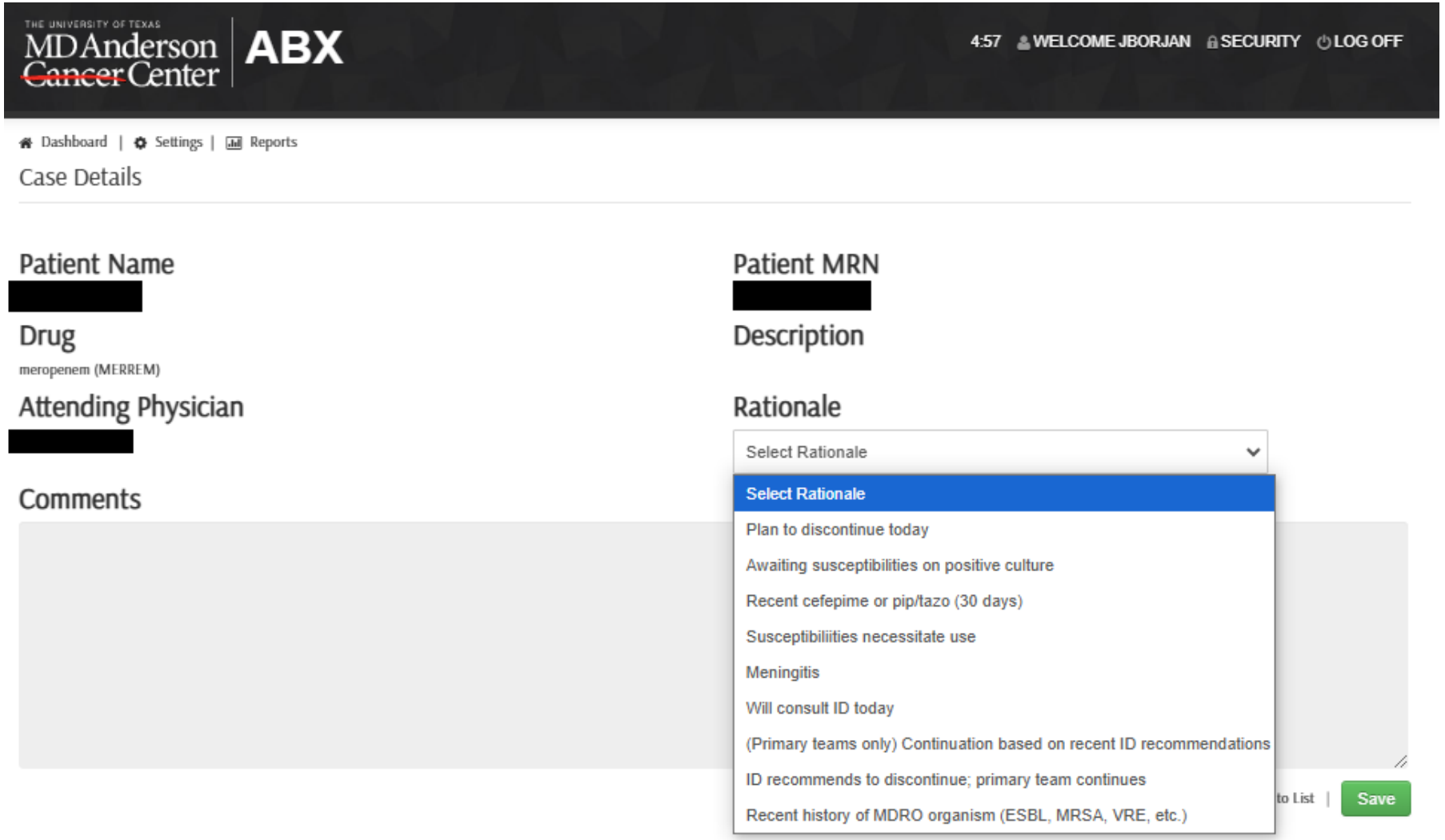
Thank you for your cooperation.

Faculty are encouraged to create an account to track/respond to their alerts at the ABX website.

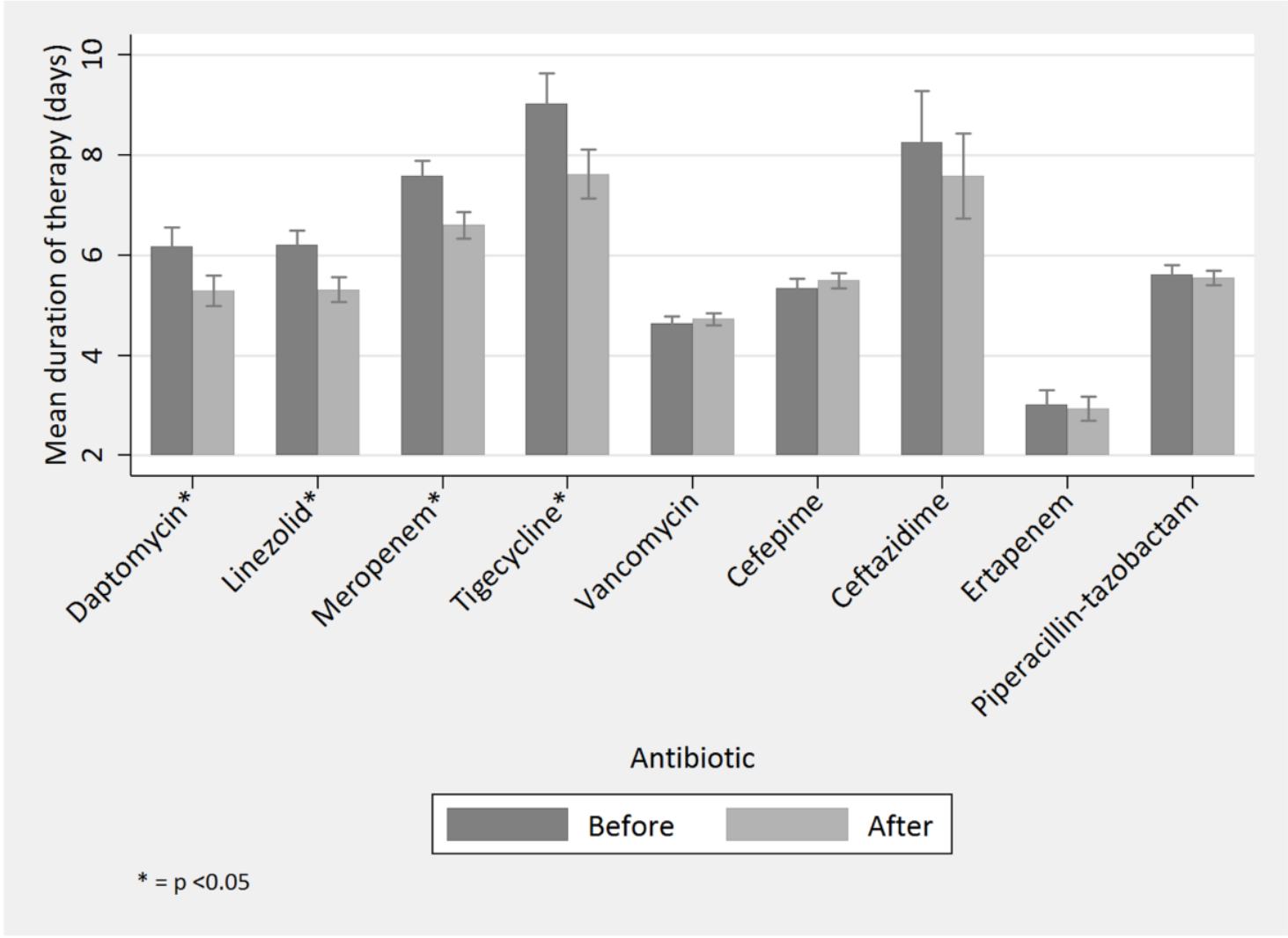
Please email the stewardship team at AntimicrobialNotification@mdanderson.org for questions/concerns

FROM: Natalie Dailey Garnes, M.D., MPH, Assistant Professor, Infectious Diseases; Director, Antimicrobial Stewardship Program

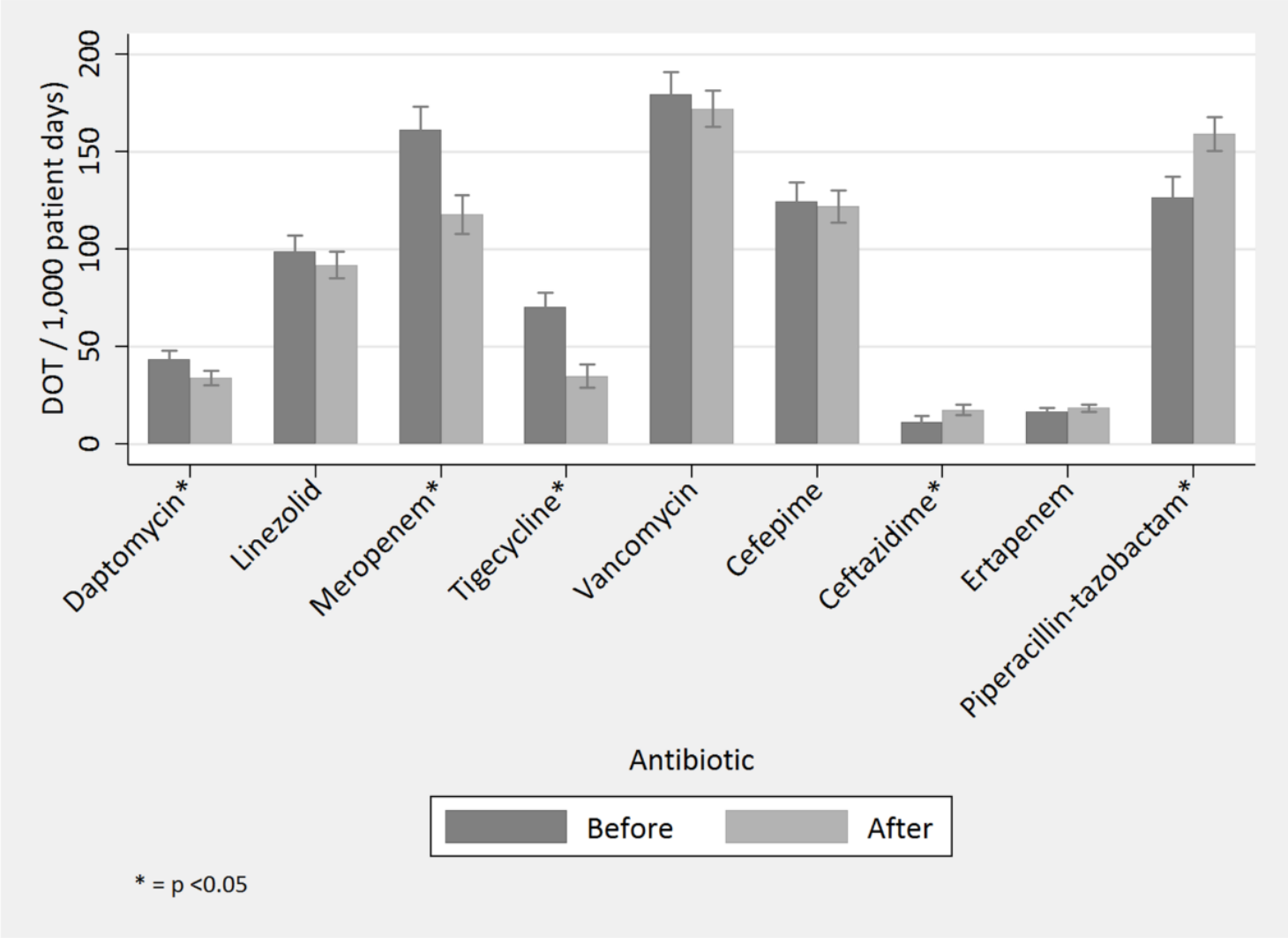
ABX Web Portal



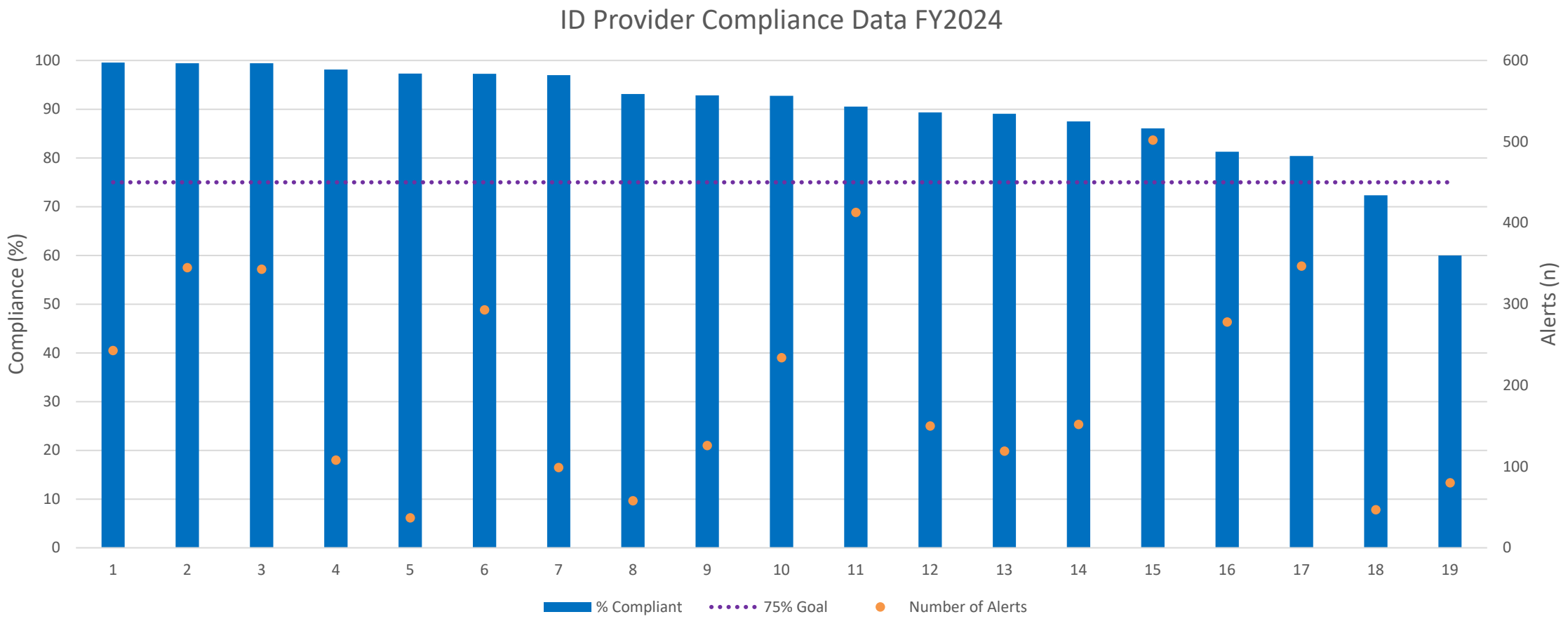
Reduction in mean duration of therapy for targeted agents



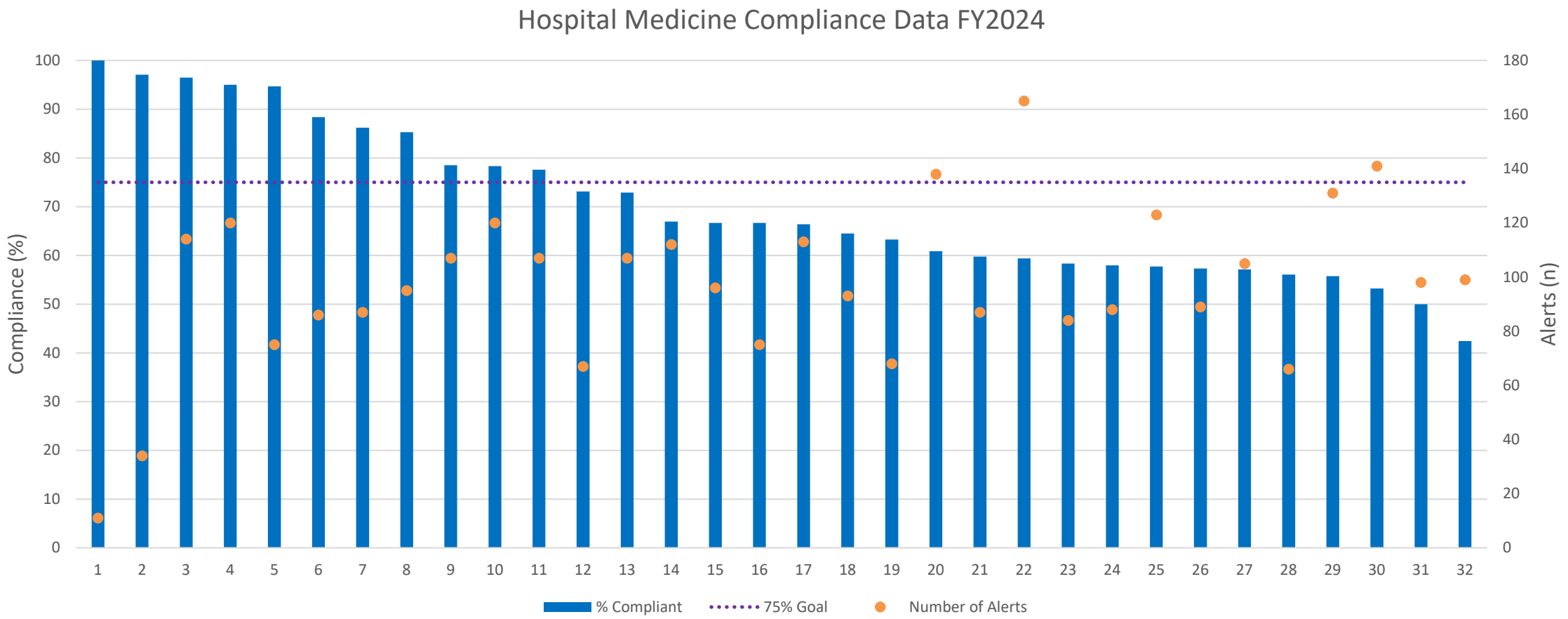
Reduction in days of therapy (DOT) per 1000 patient days



Infectious Diseases Compliance FY2024



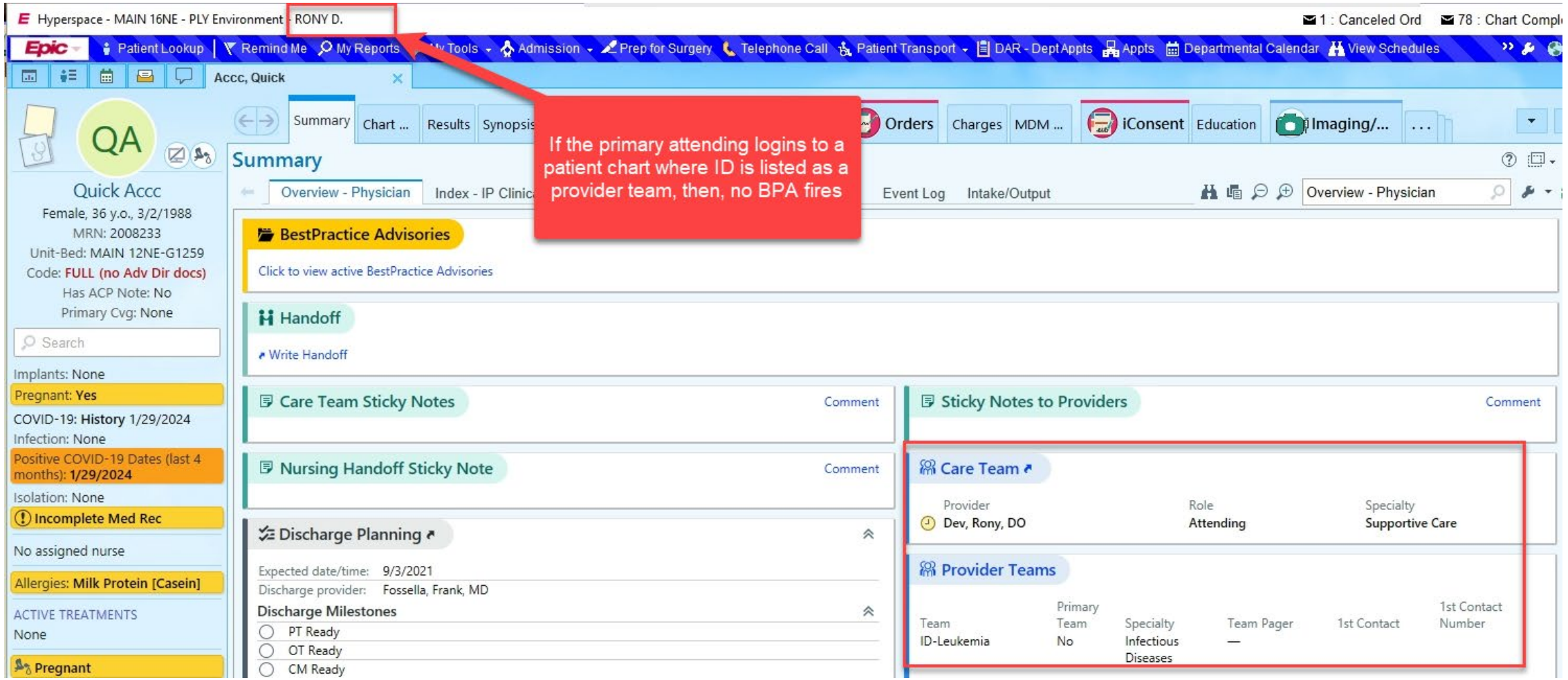
Hospital Medicine Compliance FY2024



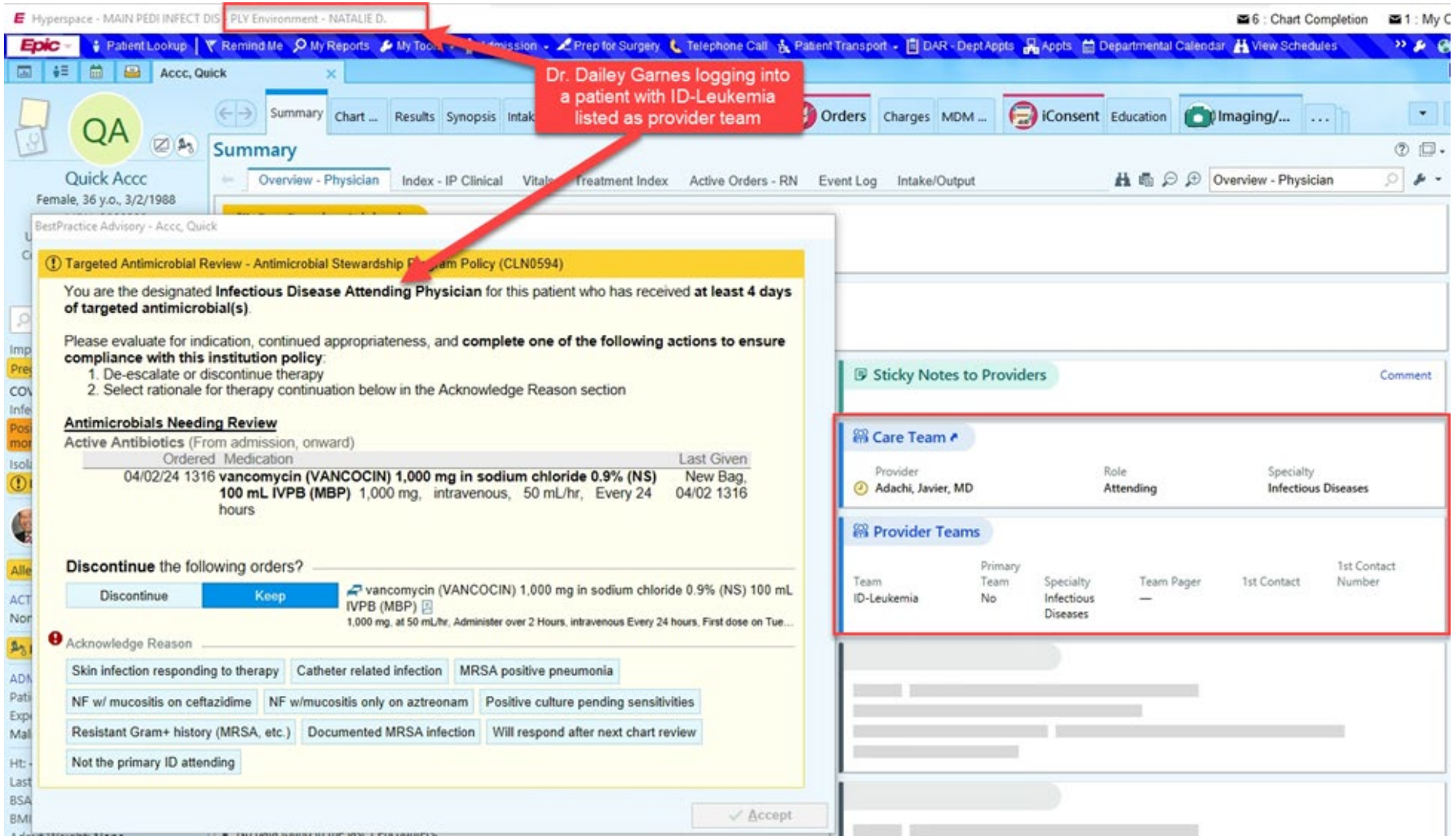
There is room for improvement and innovating the ABX model

- Providers are required to interact with a system outside of EPIC
- EPIC functionality has evolved in the years since initial ABX inception
- Project was undertaken to develop an enhanced system within EPIC
- Newer rapid diagnostics can allow for earlier assessment (day 3, 4, etc.)

Optimize alert routing for presence/absence of ID consult



Reasons for continuing therapy tailored to specific antimicrobial



Additional planned utility for new ABX system

Provider level access will have a real-time dashboard with:

- Individualized compliance rate and a departmental average comparator
- Upcoming alerts with patient and antimicrobial information

Stewardship and compliance officer level access will have a real-time dashboard with:

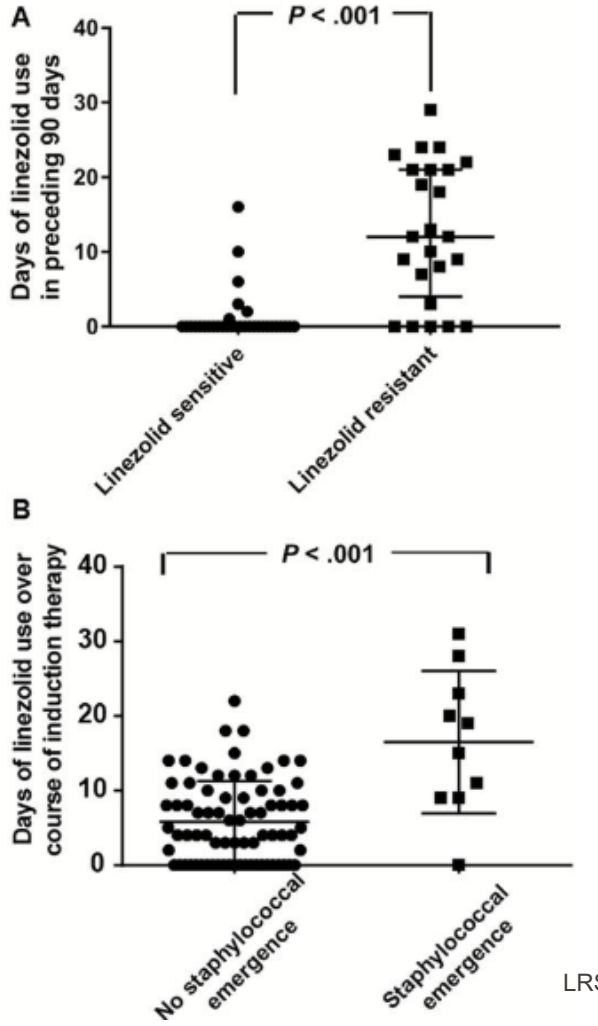
- Compliance rates of all providers individually and at the department level
  - Information on alerted antimicrobial, selected indication if continuing therapy, etc.
- Exportable data to track the most common indications selected for each antimicrobial

Interactive guidance on therapy duration modeled from initially selected indication

Combine with antimicrobial usage data to monitor and optimize service- or provider-level prescribing habits and trends

So, what about the *Staphylococcus epidermidis*?

- **A cautionary example of less than judicious use of antimicrobials**
- **Elevated linezolid use + spread of a MDR clone led to increases in LRSE in leukemia patients**
- **LRSE associated with prolonged bacteremia and numerically higher 14- and 30-day mortality**



Mulanovich VE, et al. *J Antimicrob Chemother*. 2010;65(9):2001-4.
Li X, et al. *Clin Infect Dis*. 2018;67(3):398-406.
Folan SA, et al. *Open Forum Infect Dis*. 2018;5(7):ofy167.

LRSE: linezolid-resistant *Staphylococcus epidermidis*
MDRO: multidrug-resistant organism

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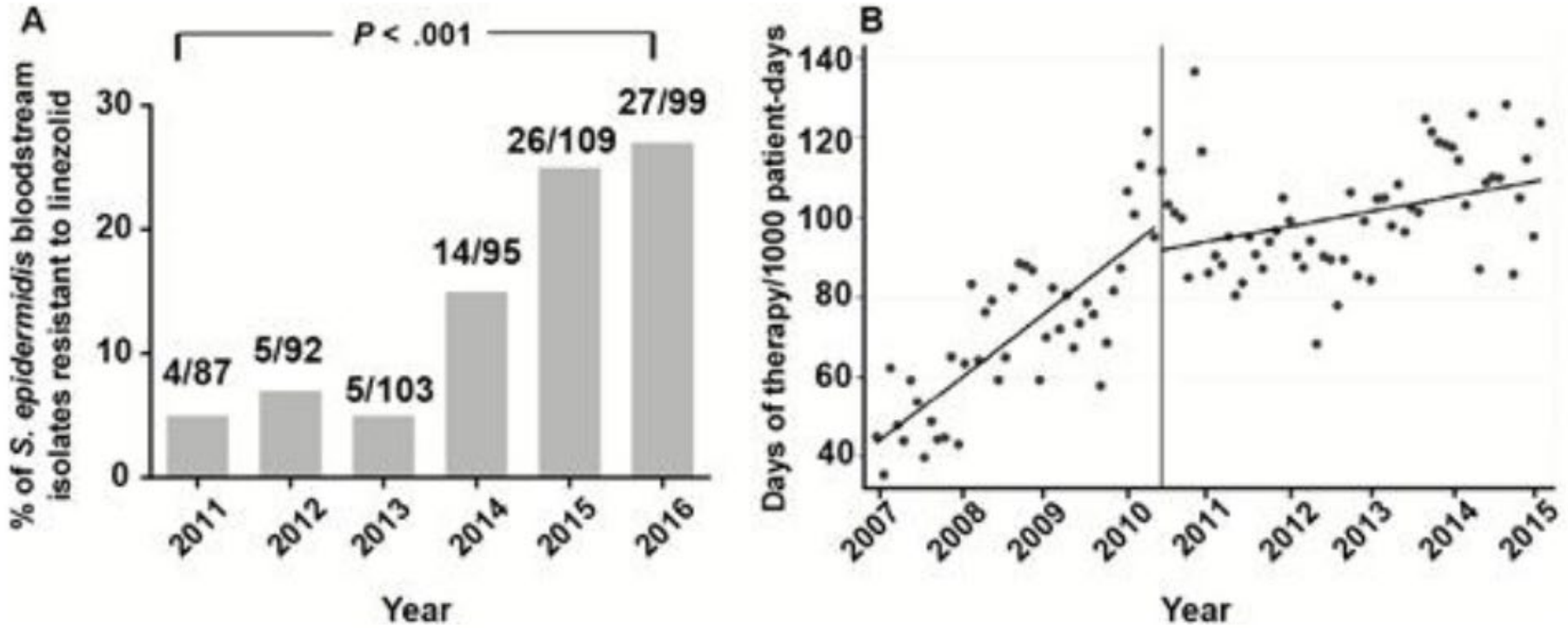

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Li X, et al. *Clin Infect Dis*. 2018;67(3):398-406.
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LRSE: linezolid-resistant *Staphylococcus epidermidis*
MDRO: multidrug-resistant organism

What interventions were employed to attempt limiting LRSE?

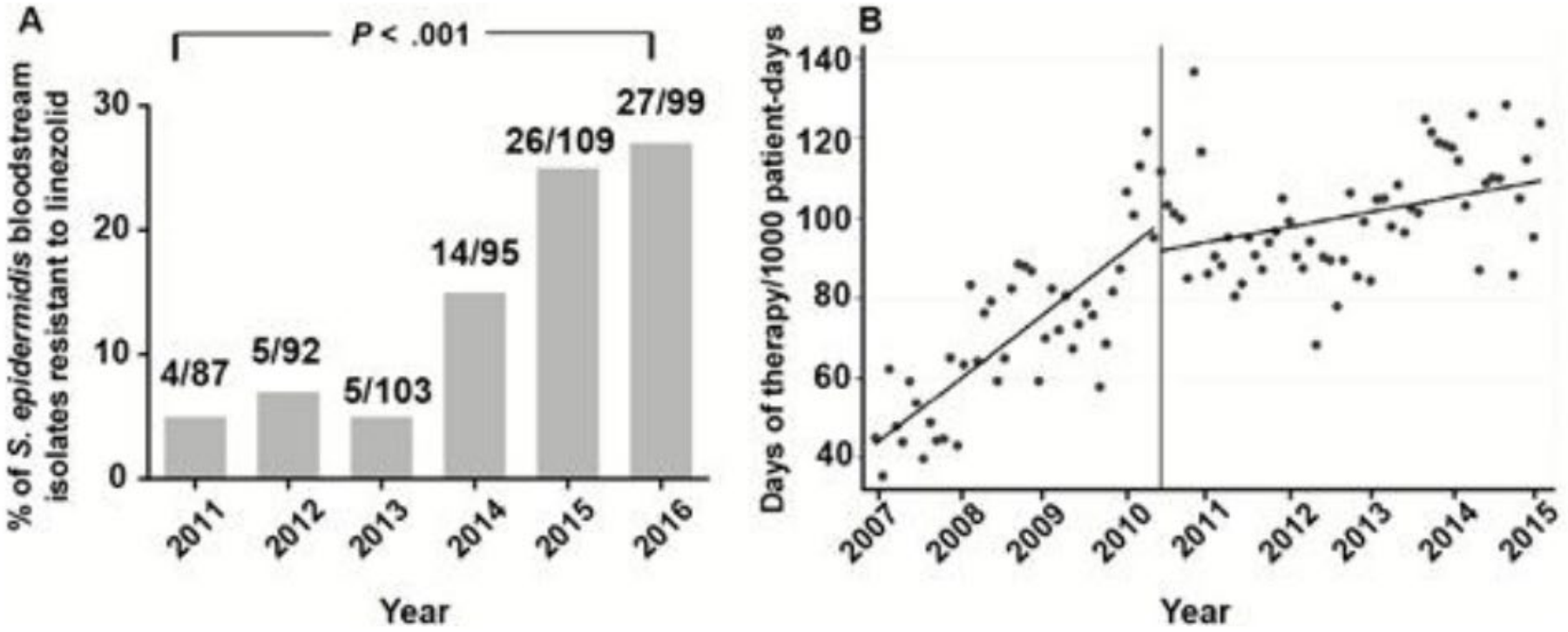
- **Specific and directed education to leukemia department**
  - Focusing on points also relevant to primary team colleagues
    - Chemotherapy delays due to prolonged bacteremia
    - Central line access complications due to necessary/unnecessary removals, exchanges, etc.
    - Potential mortality implications

- **In-person "handshake" stewardship during multi-disciplinary ID rounds paired with targeted time-outs through our ABX system to emphasize early de-escalation**
  - 13 defined daily doses (DDDs) per 100 patient-days was a potential threshold for LRSE emergence
  - Days of therapy (DOTs) per 100 patient-days is ~63% of DDDs
  - Threshold may be ~8-9 DOTs per 100 patient-days, yielding **~80-90 DOTs per 1000 patient-days**

Folan SA, et al. *Open Forum Infect Dis*. 2018;5(7):ofy167.
Vallès J, et al. *Med Intensiva (Engl Ed).* 2020 Jun-Jul;44(5):294-300.

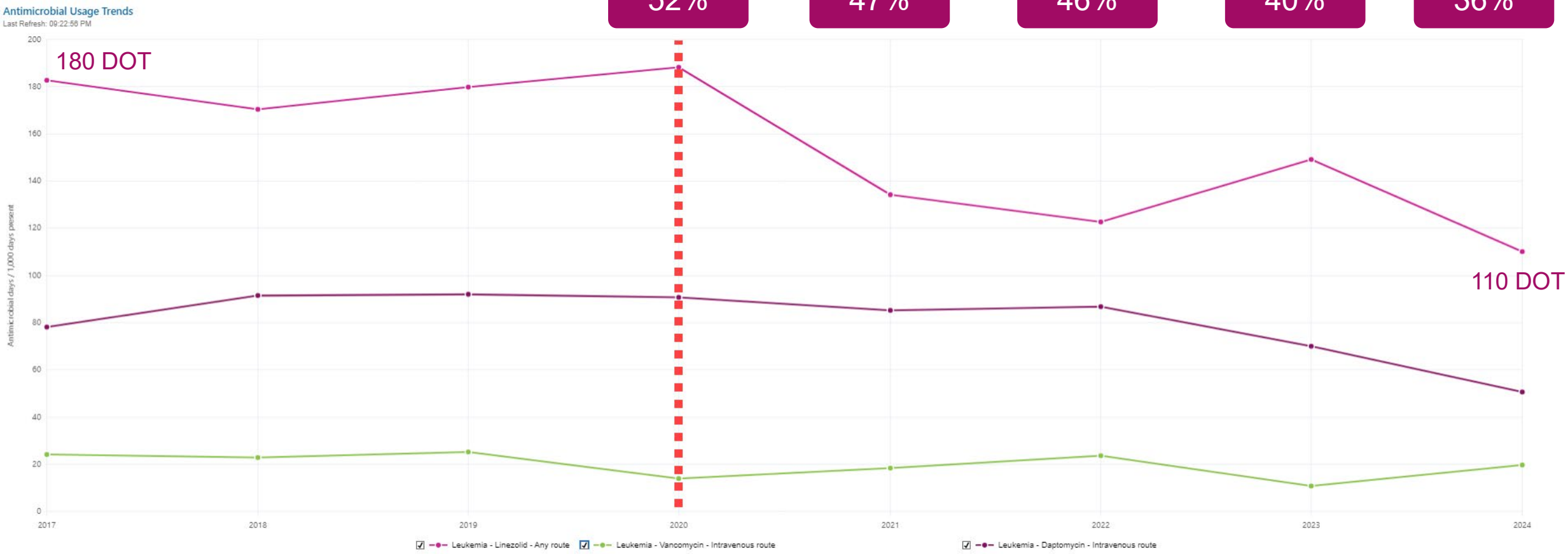
LRSE: linezolid-resistant *Staphylococcus epidermidis*

Linezolid utilization and *S. epidermidis* resistance in leukemia

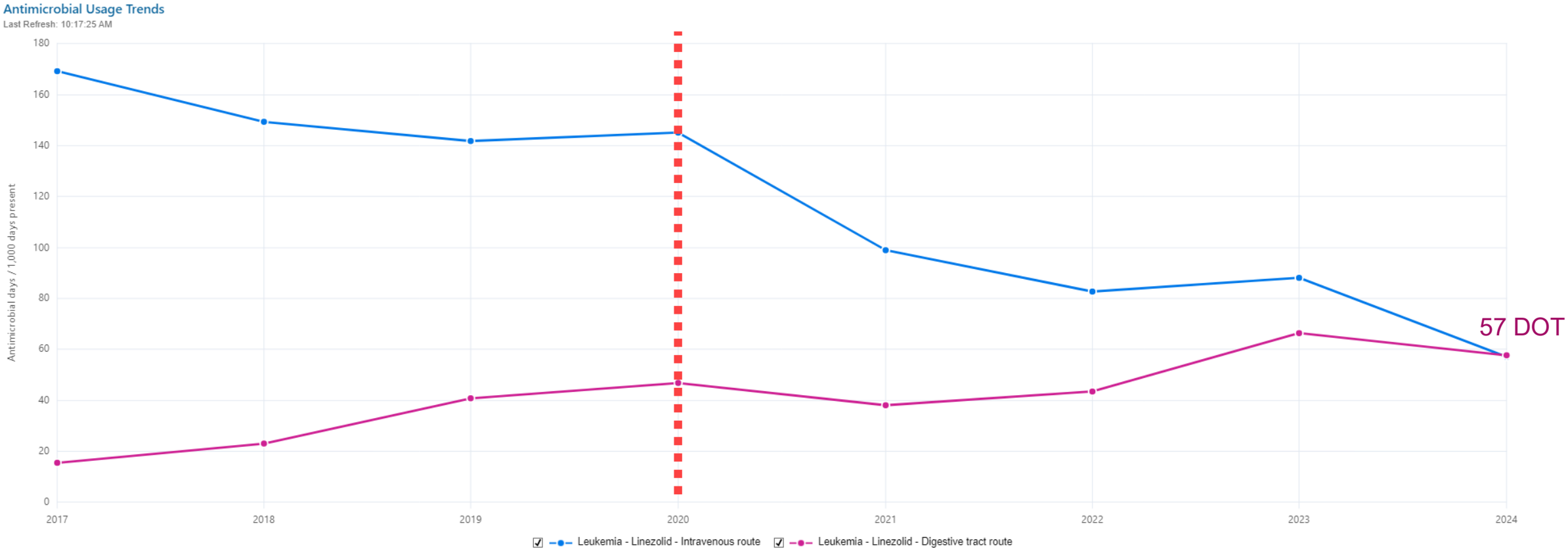


Linezolid utilization and *S. epidermidis* resistance in leukemia

2020 52% → 2021 47% → 2022 46% → 2023 40% → 2024 36%



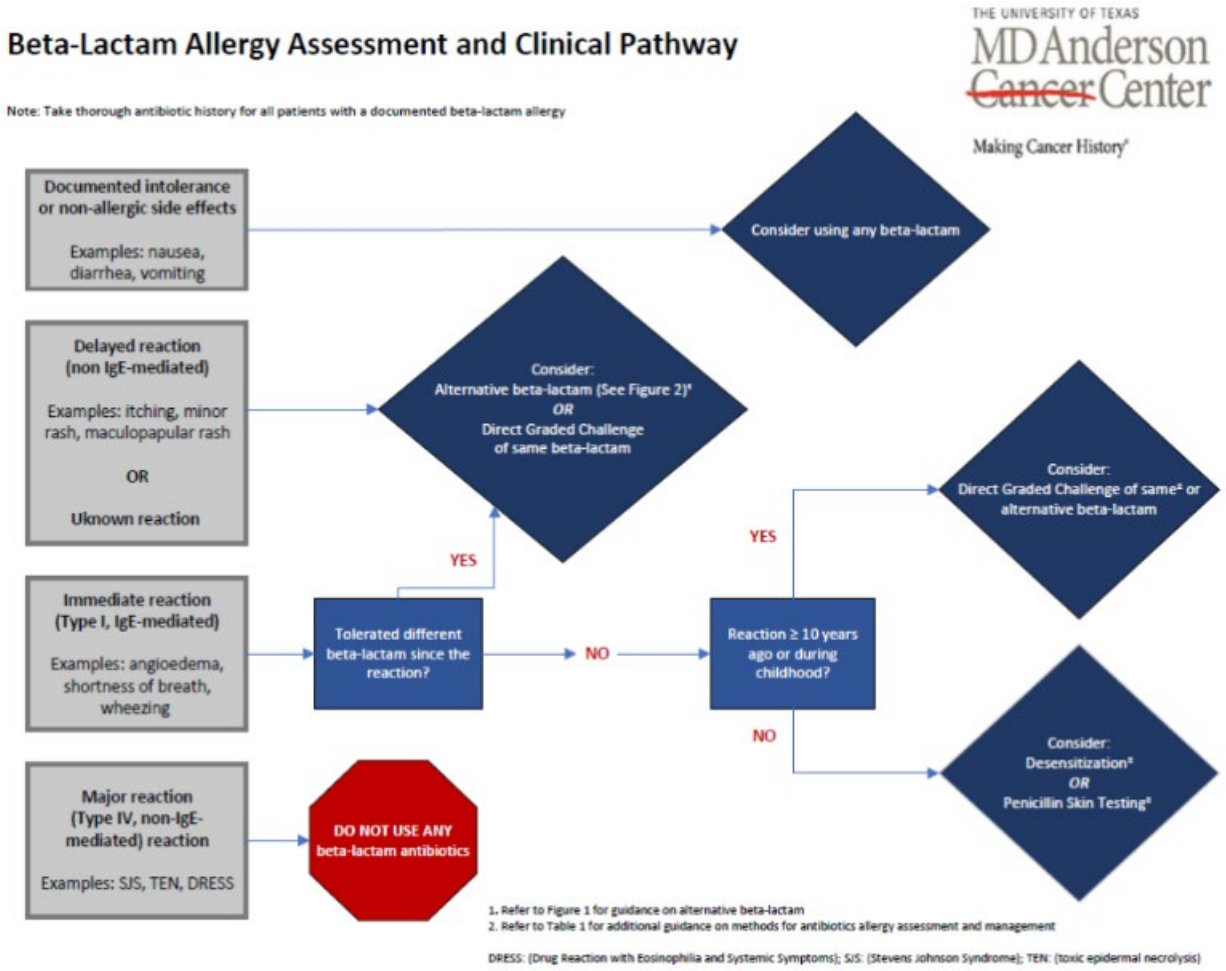
Future endeavors focused on oral linezolid prescribing



Additional stewardship interventions and future considerations

- **Outpatient parenteral antimicrobial therapy (OPAT)**

- **Antibiotic allergy de-labeling via oral and graded challenges**



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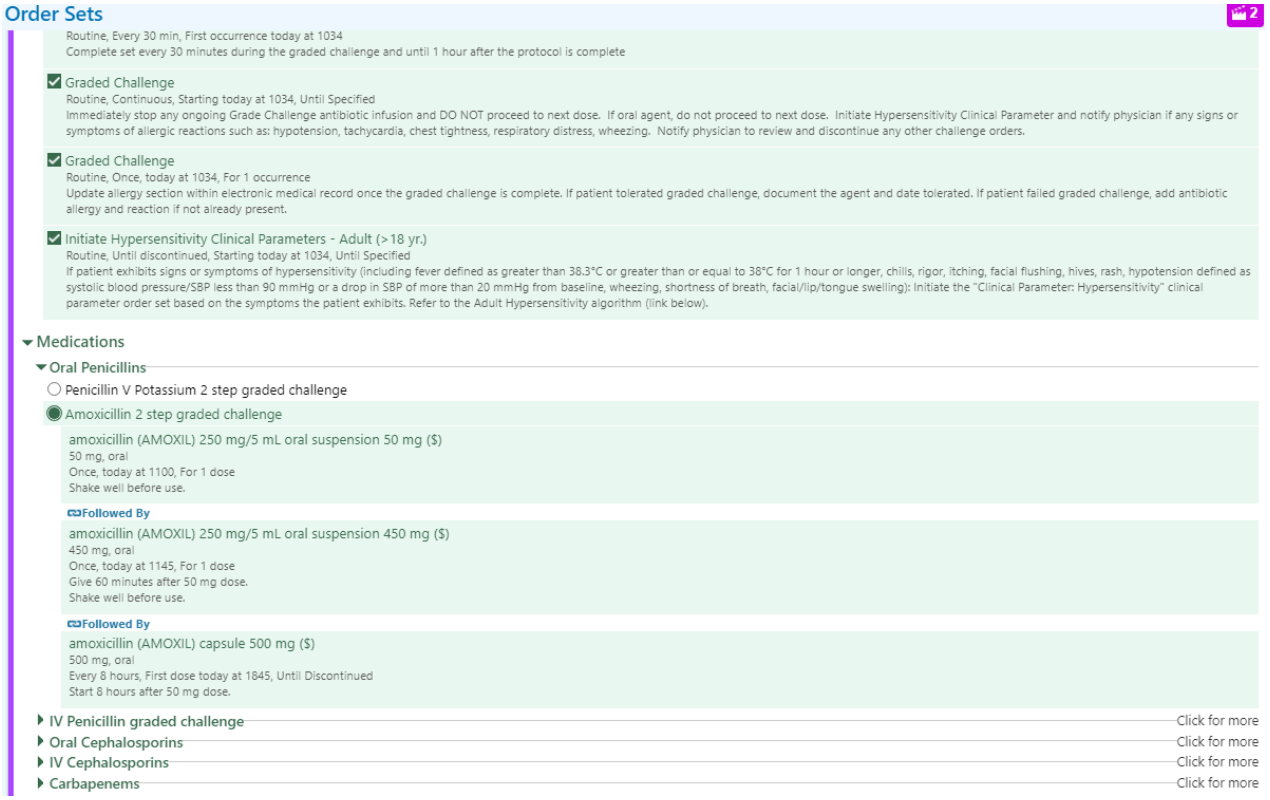
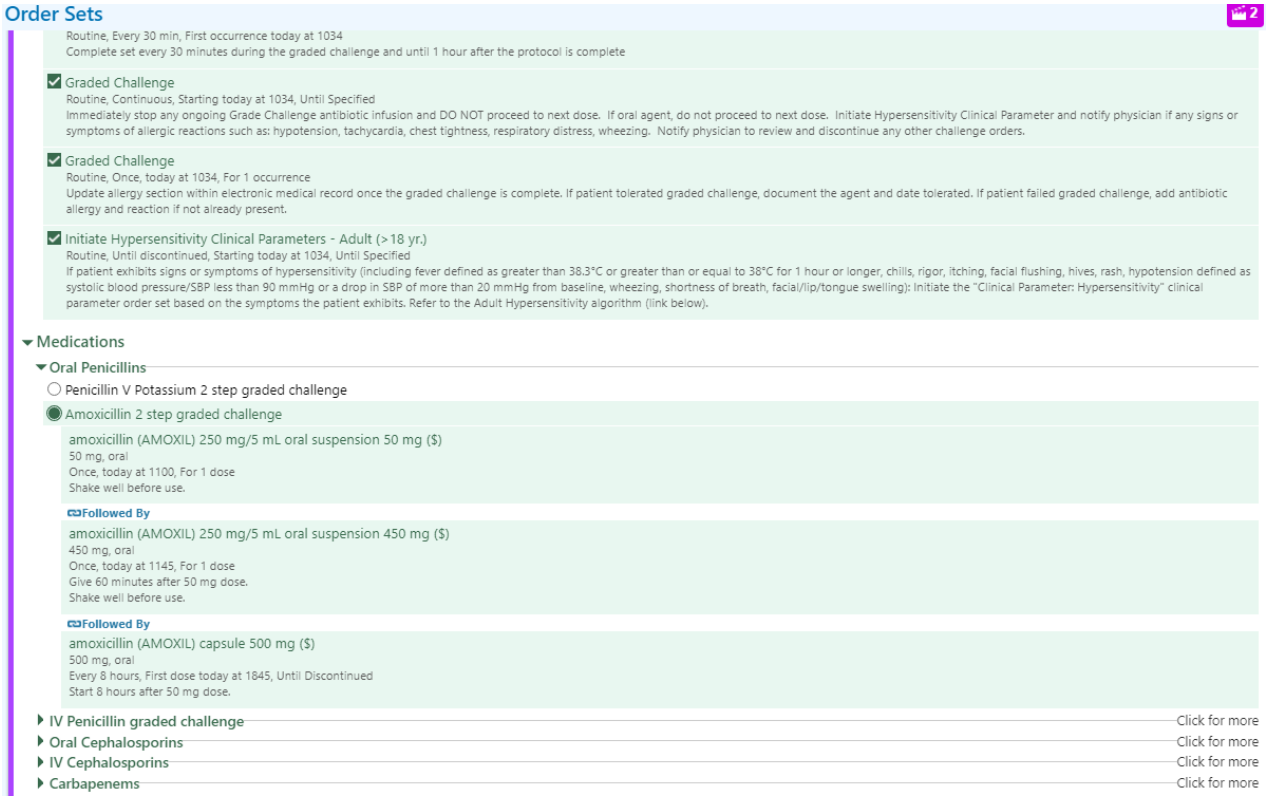


Additional stewardship interventions and future considerations

- **Outpatient parenteral antimicrobial therapy (OPAT)**
- **Antibiotic allergy de-labeling via oral and graded challenges**
- **20+ clinical algorithms across adult and pediatrics**
- **Antifungal stewardship**
- **Leveraging future developments**
  - Decolonization strategies
  - Microbiome screening and transplants
  - Phage therapies
  - Antibacterial antibodies
  - Antibody-antibiotic conjugates
  - Antibacterial vaccines
  - Machine learning



Takeaways for ABS in hematologic malignancy patients

Stewardship efforts for judicious antimicrobial escalation may be clinically warranted to ensure appropriate coverage of resistance pathogens

- Use-based restriction criteria supported by best available data
- Bolstered with in-person rounding/"hand-shake" stewardship + prospective audit and feedback

Easier buy-in for indication-based continuation of therapy efforts than indication-based initiation of therapy?

- Innovating on traditional antimicrobial time-outs may result in more appropriate and timely de-escalation
- Interactive guidance on suggested therapy durations modeled from initially selected continuation indication
- Monitoring and optimization of service- or provider-level prescribing trends

Collaborate with and recruit stakeholder support from non-ID specialists

- Identify data points and outcomes which are important to both parties

Acknowledgements

- **Current AMS team**
  - Natalie Janine Dailey Garnes, MD
  - Eduardo Yepez, MD
  - Micah Bhatti, MD, PhD
  - Nancy Vuong, PharmD
  - Jovan Borjan, PharmD
  - Josh Hendrickson, PharmD
  - Meghan Kamath, PharmD
  - Kevin Lin, PharmD
  - Kelsey Olson, PharmD
  - Alex Stabler, PharmD
- **Past ID PharmDs**
  - Frank Tverdek, PharmD
  - Sam Aitken, PharmD
  - Patrick McDaneld, PharmD
  - Farnaz Foolad, PharmD
  - Emily Fox, PharmD
  - Jaime Peña, PharmD
- **ID physicians, particularly**
  - Roy Chemaly, MD
  - Victor Mulanovich, MD
  - Issam Raad, MD
  - Dimitrios Kontoyiannis, MD
  - Javier Adachi, MD
  - Bruno Granwehr, MD
  - Amy Spallone, MD
- **Infection Control**
- **Microbiology Lab**
- **Shelburne Lab**
  - Sam Shelburne, MD
  - Will Shropshire, PhD
  - Chin-Ting Wu, MS
  - Others
- **Other collaborators**
  - Meagan Rowan, PA-C
  - Primary team PharmDs
  - Kenneth Rolston, MD
  - Emma Dishner, MD
  - Jalen Bartek, RN
  - AskMDAnderson

Many, many others involved in projects over the years

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