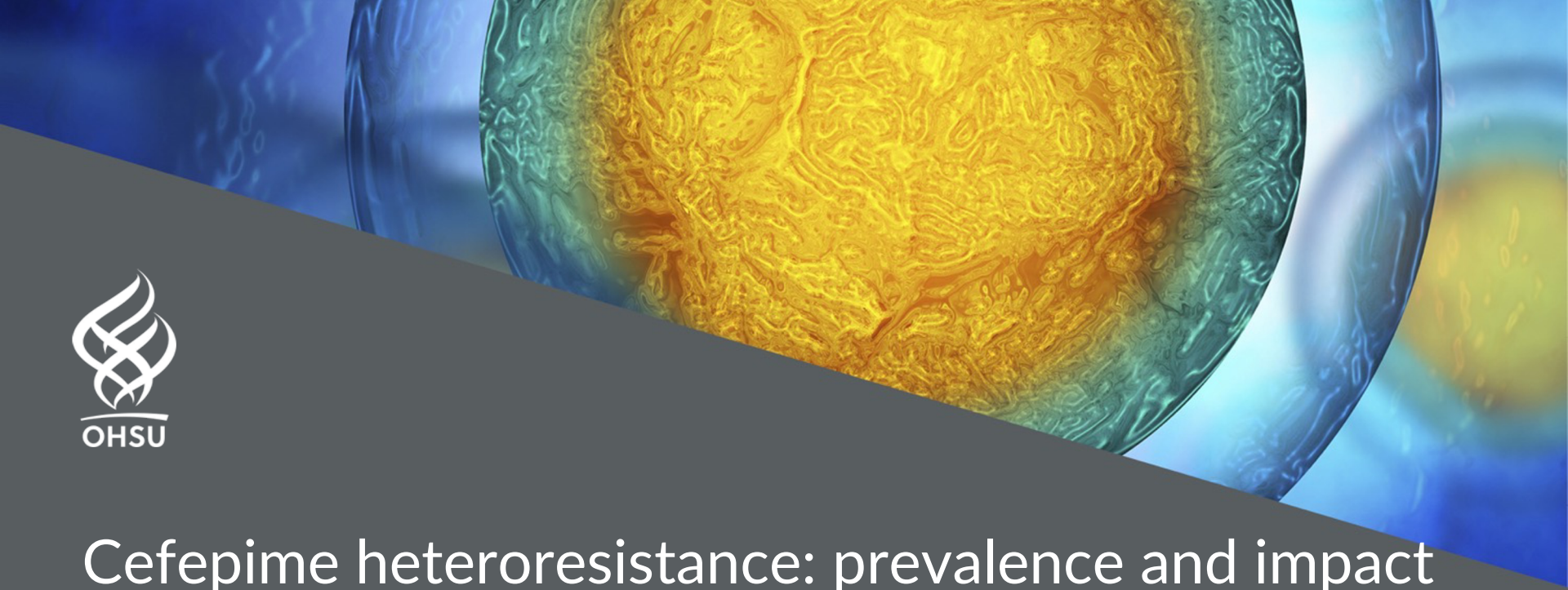


Cefepime heteroresistance: prevalence and impact across *Pseudomonas aeruginosa* bloodstream isolates in patients with hematologic malignancies

DATE: JAN 17, 2024

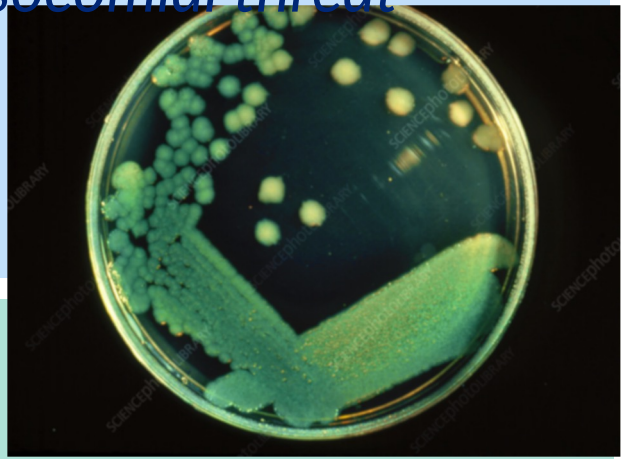
PRESENTED BY: STEPHANIE L. EGGE, MD

Pseudomonas aeruginosa: *leading AMR nosocomial threat*

Multi-drug resistant *Pseudomonas aeruginosa*

- 32,600 infections among hospitalized
- 2,700 attributed deaths

- Center for Disease Control, AMR Report 2017.



Significant source of morbidity and mortality

- Bacteremia – all patients [1]
- Hematologic malignancy and neutropenic fever [2,3]

- Prompt choice of *effective* antimicrobial therapy is imperative [1,4]

- **Cefepime**, choice neutropenic fever regimen of most facilities here in the US [4]
  - Most hospital antibiograms report ~92% cefepime susceptibility across *P. aeruginosa* isolates
    - β-lactam exposure increases risk for resistance emergence (P=0.035) [5]

[1]Micek et al, AAC 2005. [2]Tofas et al, Diagn Microbiol Infect Dis 2017. [3]Satlin et al, JAC 2017. 4 Chumbita, JAC 2022.
[5] Akhabue et al, Emerg Infect Dis 2011.

Questions of cefepime efficacy

All-cause mortality increase in *some* meta-analyses

- Yahav et al, Lancet Infect Dis 2007. **RR: 1.26 [95% CI 1·08–1·49]**

Some studies acknowledge that in the setting of prolonged neutropenia cefepime monotherapy is associated with failed blood culture clearance and higher rates of bacteremia recurrence

- Mebis et al, Lancet Infect Dis 2009.
- Jandula et al, Chemotherapy 2001.

Questions of AST and optimal dosing

Optimization of dosing has posed questions and challenges

Rich et al, Obes Surg, 2012.
Burgess et al, Annals of Pharmacotherapy 2015.

Advent of resistance in Enterobacterales has already demonstrated how **prior breakpoints have failed to capture concerns for emerging β-lactamase resistance**

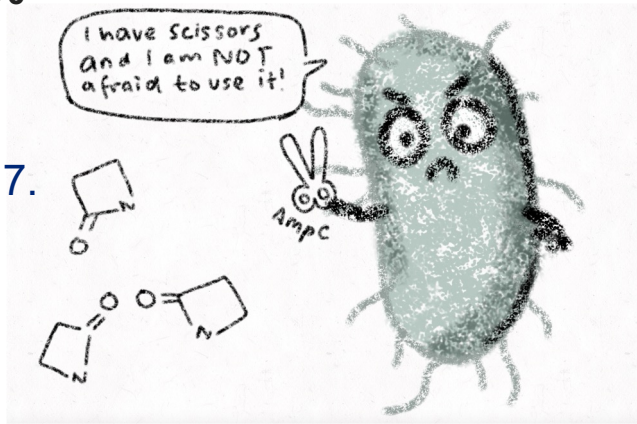
Lee et al, CID 2012

Questions of cefepime efficacy with elevated MICs

P. aeruginosa isolates with MICs 4 -8 µg/ml: <u>independent risk factors for mortality/recurrence</u>

- 4µg/mL cut-off **76.5% mortality rate vs. 27.4%**
- *Only protecting factor here was to maximize cefepime dosing*

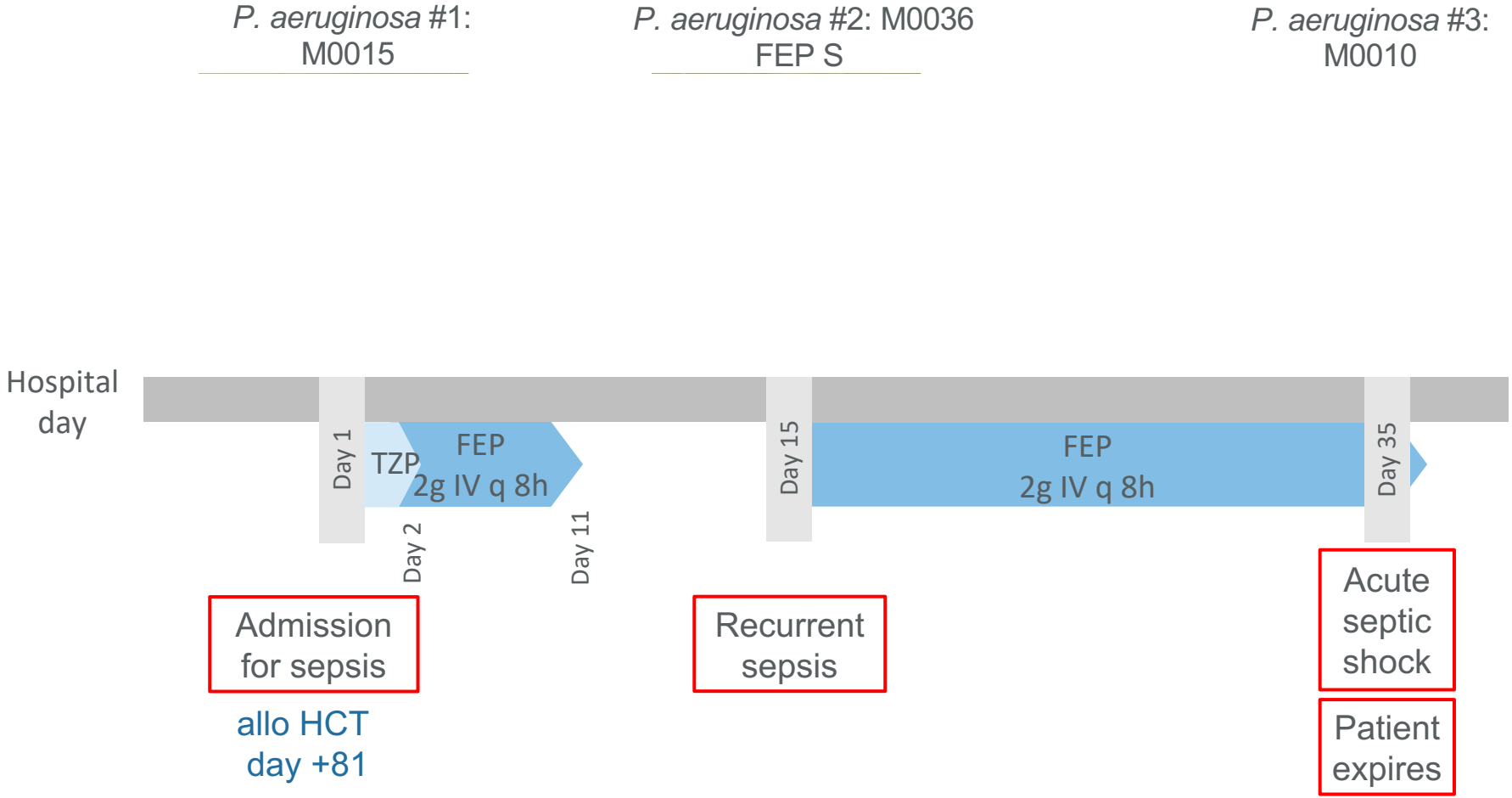
Su et al, Ann Clin Microbiol Antimicrob 2017.



MIC of 8µg/mL associated with increased 28-mortality, P = 0.002; **adjusted OR, 9.1**; 95% CI, 2.2 to 37.5

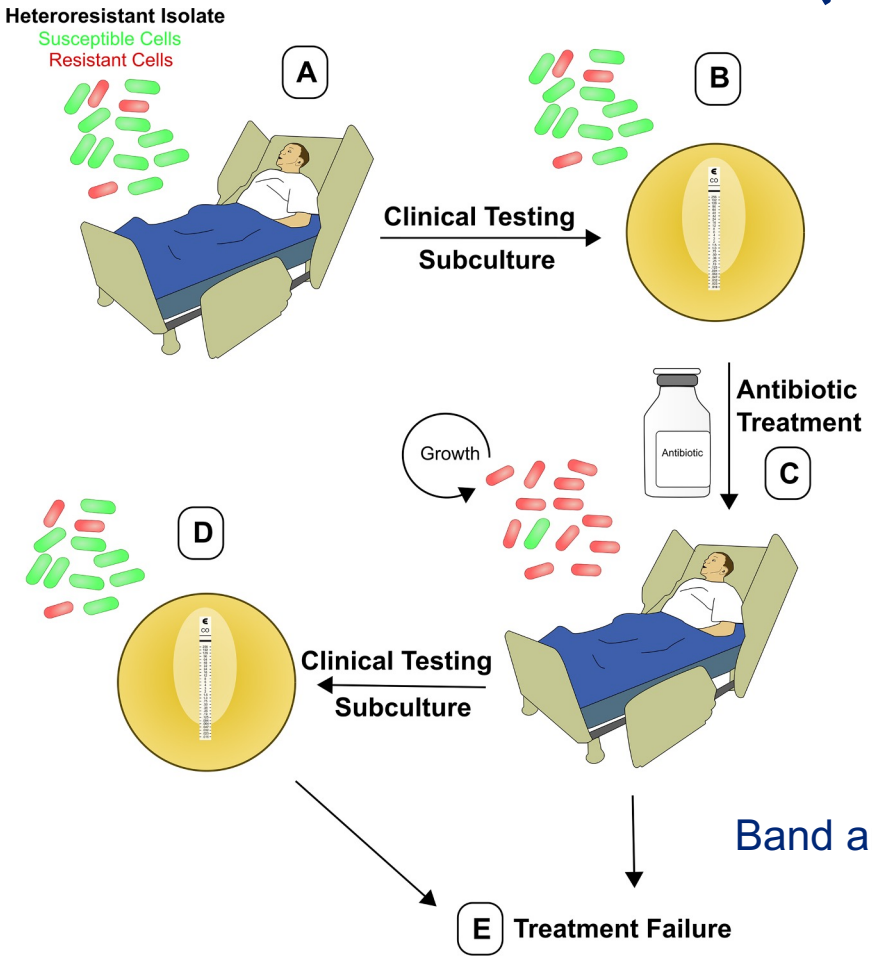
- *Independent of dosing regimen*

Bhat et al, AAC 2007.



Abbreviations: TZP - piperacillin-tazobactam; FEP - cefepime

Heteroresistance (hR)



- single lineage isolate displays multiple subpopulations of varying antibiotic susceptibility/resistance
- Not detectable/defined by standard antimicrobial susceptibility testing methods
  - One possible explanation for clinical outcome and laboratory discrepancies

Band and Weiss, PLoS Pathogens 2019.

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Cefepime heteroresistance (FEP-hR)

Jia et al, 2020.

ELSEVIER
International Journal of Antimicrobial Agents
Volume 55, Issue 3, March 2020, 105832

Heteroresistance to cefepime in *Pseudomonas aeruginosa* bacteraemia

Single center study 2011-2016 assessing FEP-hR across all clinical bloodstream isolates of *P. aeruginosa (*n=192)

- >50% prevalence
- hR independent association with hematologic malignancy (RR: 2.37 P-value: 0.016)
- Higher treatment failures (RR: 2.08, P-value 0.035)

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Cefepime heteroresistance (FEP-hR)

Table 1. Clinical data and minimum inhibitory concentrations for cefepime heteroresistance (FEP-HR) in *Pseudomonas aeruginosa* bacteraemia.

Isolates	Date	MIC of native population (mg/L)					
		IPM	MEM	FEP	CAZ	GEN	CIP
PA-6005	05-2015	0.25	0.5	4	8	1	0.25
PA-6008	10-2015	0.25	0.25	2	2	1	0.25
PA-6025	12-2015	1	0.5	2	4	1	0.25
PA-6026	01-2016	0.5	1	8	16	1	0.25
PA-6034	02-2016	0.25	0.5	4	8	0.5	0.25
PA-6043	04-2016	0.25	0.5	4	4	0.5	0.125
PA-6052	07-2016	1	0.25	2	4	1	0.25
PA-6058	12-2016	0.25	0.25	8	8	0.5	0.125

Jia et al, 2020.

We hypothesized that FEP-HR *P. aeruginosa* bloodstream infections are common among patients with malignancy.

Suspect that this phenomenon contributes to observed treatment failures, recurrent bacteremias, and resistance emergence.

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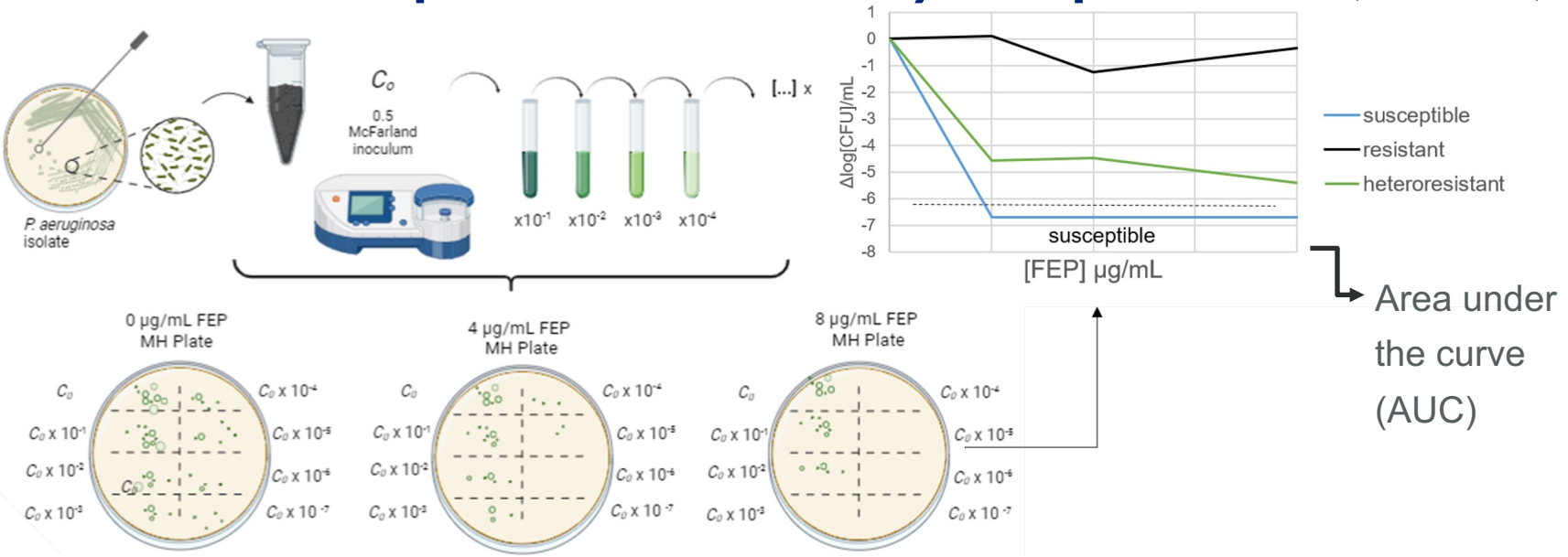
Methods: Population analysis profile (PAP)



- Resistant: greater than 50% of initial inoculum growth is seen at the antibiotic break point
- Heteroresistant: ≥1/10^6 bacterial growth occurs at 1-2x the antibiotic breakpoint

Band and Weiss, 2021.

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Breakpoints for *P. aeruginosa*

	Broth Microdilution/Etest (µg/mL)				Kirby-Bauer Disk Diffusion Diameter (mm)		
Resource	**S**	**I**	**R**		**S**	**I**	**R**
CLSI M100	≤8	16	≥32		≤14	15-17	≥18
EUCAST	≤8		>8		≥21		<21
FDA	≤8		≥16		≥18		<17

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Example cases of failure on our hematopoetic stem cell transplant service

Patient 1: HCT +81 days

P. aeruginosa #1:M0015
FEP S

MIC 4 µg/mL

FEP
2g IV q 8h

P. aeruginosa #2:M0036
FEP S

MIC 4 µg/mL

FEP
2g IV q 8h

P. aeruginosa
#3:M0010
FEP R; TZP R

MIC ≥ 16
µg/mL

Patient 2: Neutropenic fever pre-HCT s/p FLAG-ida

P. aeruginosa #1: M0067
FEP S

MIC 1 µg/ml

FEP
2g IV q 8h

P. aeruginosa #2:
M0025
FEP R (per BMD)

MIC ≥ 16 µg/ml

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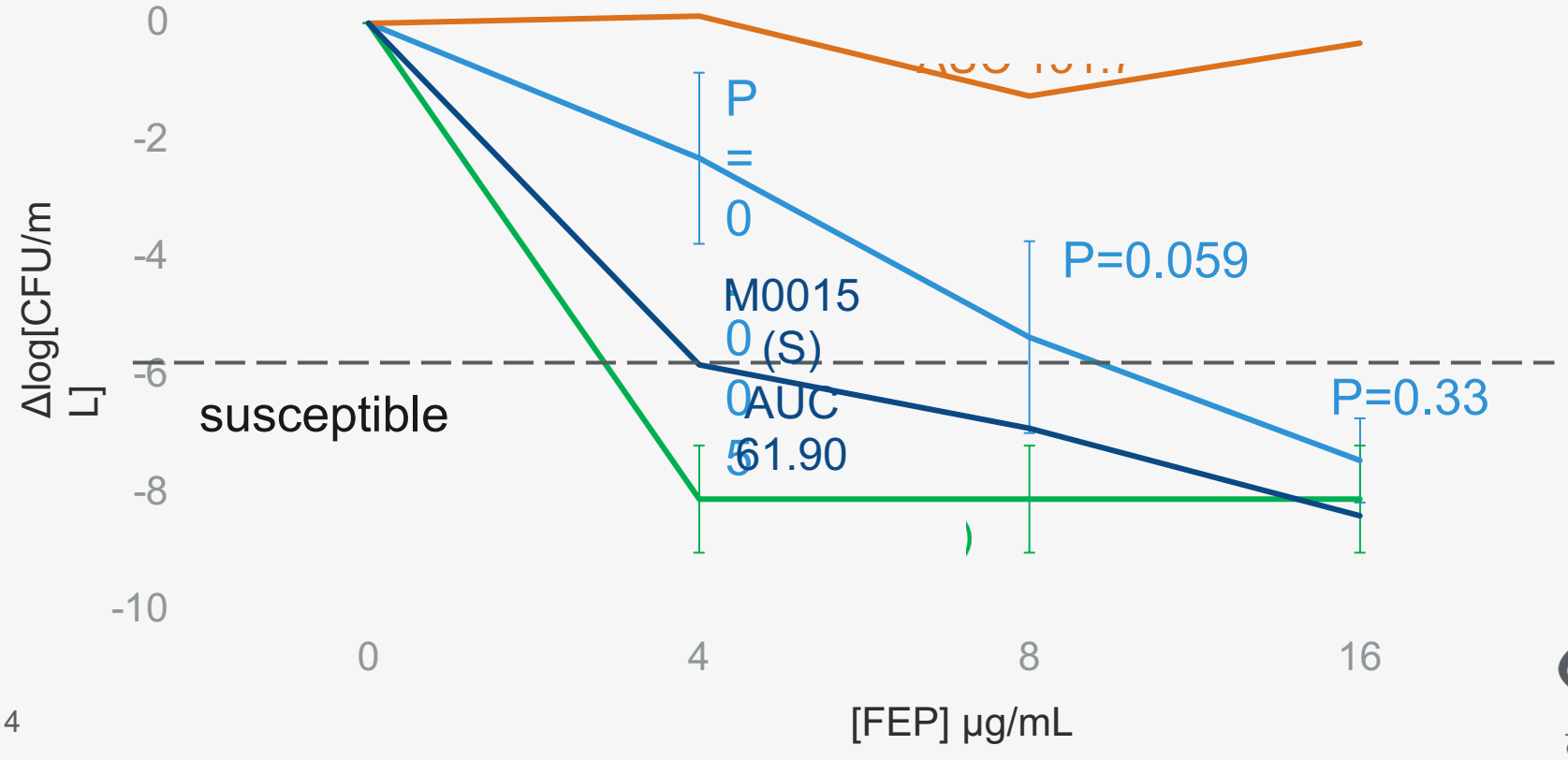
PAP-AUC detects a quantifiable significant difference between problematic clinical hR isolates and susceptible controls



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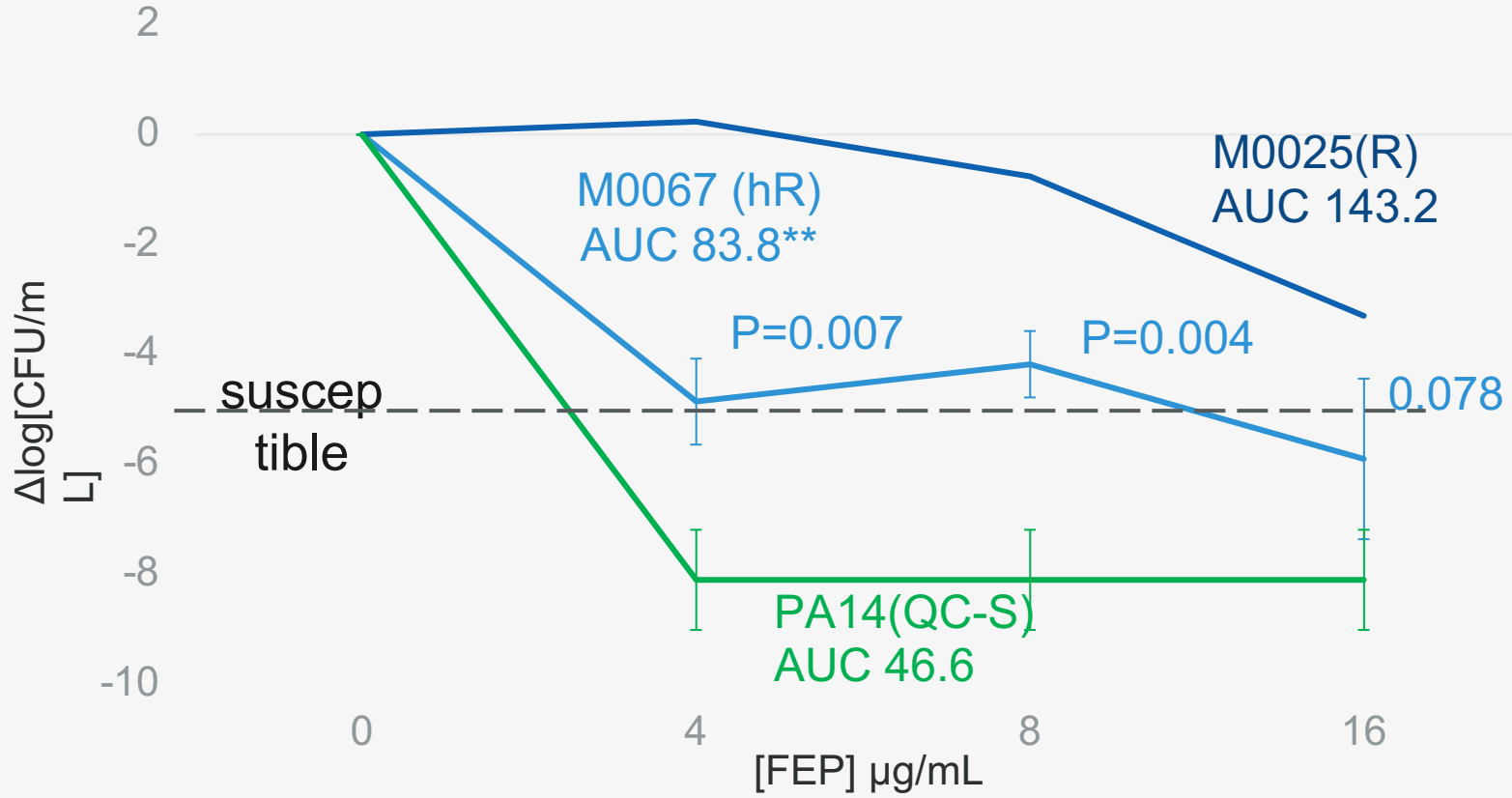

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Populations that survive at the breakpoint demonstrate decrease in KB disk diameter

*P<0.05,
**P<0.01

M0067	M0067	M0025
sub 0 µg/mL	sub 8 µg/mL	*from stock*
24h KBDD	24h KBDD	24h KBDD
31 mm	19 mm*#	19 mm#
MIC 1 µg/mL	MIC 4 µg/mL**	MIC > 16 µg/mL

#EUCAST resistant classification

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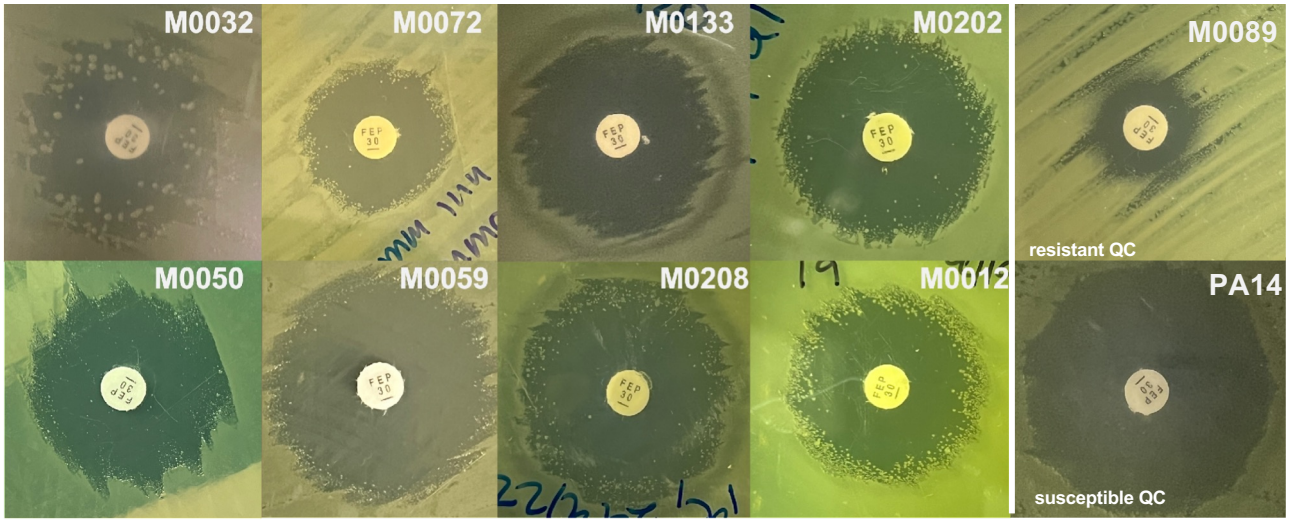
QC per AST standard for S/R



	No. of Isolates (n=24)	%
hR detected at 24 hours	4	16.7%
hR detected at 48 hours	15	62.5%

Pseudomonas aeruginosa cefepime heteroresistance screen per KB to date bloodstream isolates from HM patients

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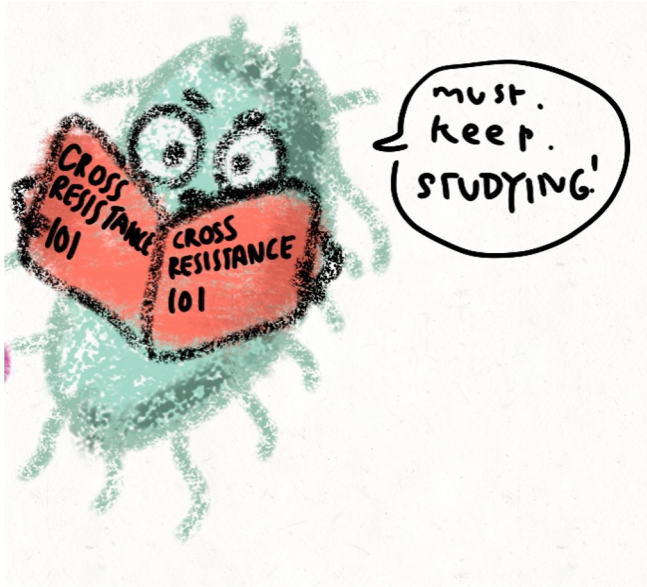
Future work

- PAP-AUC survey with subculture analyses to detect AUC cutoffs for persisters versus hR and clinical relevance
  - Growth curves of subs in presence of antibiotic to determine if stationary/quiescent or growth phase
- WGS and transcriptomic analysis comparing phenotypes and progression



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