Ceftazidime-avibactam Activity against *P. aeruginosa* from Intensive Care (ICU) and Non-ICU Patients

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Some JMI employees are advisors/consultants for Allergan, Astellas, Cubist, Pfizer, Cempra, and Theravance.

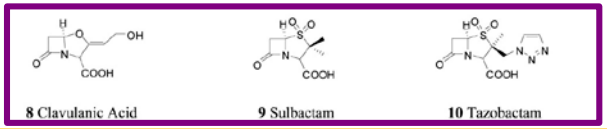
Ceftazidime-avibactam (AstraZeneca/Allergan)

- Ceftazidime is a well described third-generation cephalosporin with broad-spectrum activity
- Avibactam (formerly NXL-104) is a member of a novel class of non-β-lactam β-lactamase inhibitors, the diazabicyclooctanes (DBOs)
- Avibactam can effectively inactivate:
  - Class A: ESBL and KPC
  - Class C: AmpC
  - Some Class D: OXAs

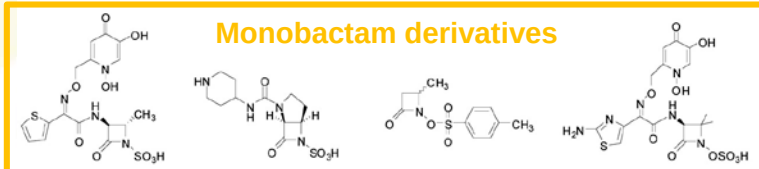
β-lactamase Inhibitors

JMI LABS

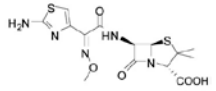
Clinically available

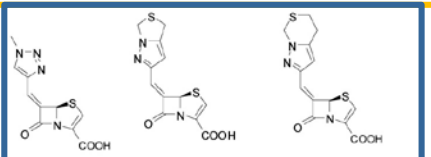


Monobactam derivatives

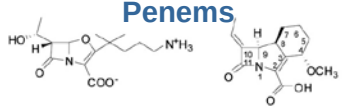


Penicillin derivative

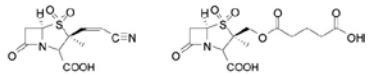




Penems

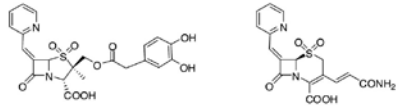


Penam Sulphones

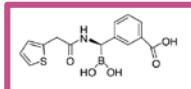


Drawz & Bonomo, CMR 2010; 23:160-201

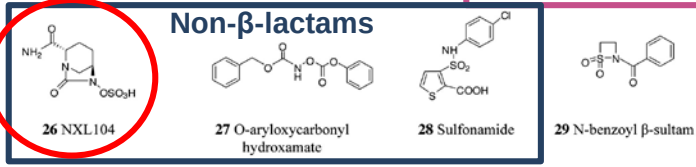
Penam Sulphones

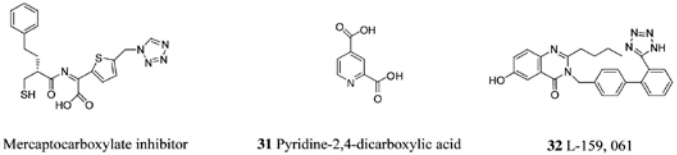


Boronic acid transition state analog

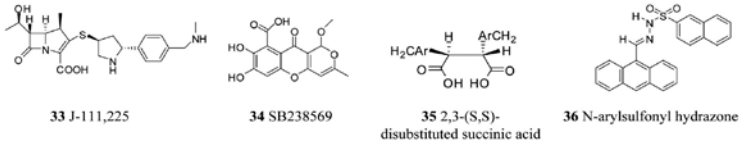


Non-β-lactams





MBL inhibitors



Avibactam

- Avibactam is a non-β-lactam diazabicyclooctane (DBO)
- Prolonged deacylation rate (slow deacylation through hydrolysis or reversibility)

$$E + I \rightleftharpoons EI \rightleftharpoons EI^*$$

- Using a model for slow binding enzymes demonstrated that formation of EI and EI* is fast and more efficient than β-lactam-based BLI

Ehmann et al. PNAS 2012; 129:11663-8.

Spectrum of Activity of Avibactam

β-Lactamase		Clavulanate	Tazobactam	Avibactam
Class A	TEM, SHV and ESBLs	√	√	√
	CTX-M and ESBLs	√	√	√
	PER, VEB, GES	√	√	√
	KPC	X	X	√
Class B	IMP, VIM, NDM	X	X	X
Class C	Chromosomal *Enterobacteriaceae* AmpC	X	X	√
	Chromosomal *Pseudomonas* AmpC	X	X	√
	Plasmidic ACC, DHA, FOX, LAT, MIX, MIR, ACT	X	X	√
Class D	Penicillinase-type OXA-1, -31, -10, -13	Variable OXA-1, -10	Variable	Variable OXA-1, 31
	Carbapenemase-type OXA-23, -40, -48, -58	Variable	Variable OXA-23, -48	Variable OXA-48

Ceftazidime-avibactam (AstraZeneca/Allergan)

- Ceftazidime-avibactam has been approved by the US FDA and the European Medicine Agency to treat:
  - Complicated intra-abdominal infections (in combination with metronidazole)
  - Complicated urinary tract infections, including pyelonephritis
  - Hospital-acquired pneumonia, including ventilator-associated pneumonia (Europe only)
- Dosage: 2,000/500mg q8h (2h infusion)

Objectives

- To compare the antimicrobial susceptibility patterns of *P. aeruginosa* isolated from ICU and non-ICU patients
- To evaluate the *in vitro* activity and antimicrobial spectrum of ceftazidime-avibactam

Materials and Methods

Bacterial Isolates

- Collected in 2013-2015 as part of the International Network for Optimal Resistance Monitoring (INFORM) Program
- 72 medical centers among 37 states from all nine US Census divisions
- Consecutive collected bacterial isolates from various infections
- Isolates determined significant by local criteria as reported probable cause of infection
- The INFORM Program only evaluates the antimicrobial susceptibility of Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*
- Species identification confirmed by standard biochemical tests and MALDI-TOF, when necessary

Materials and Methods

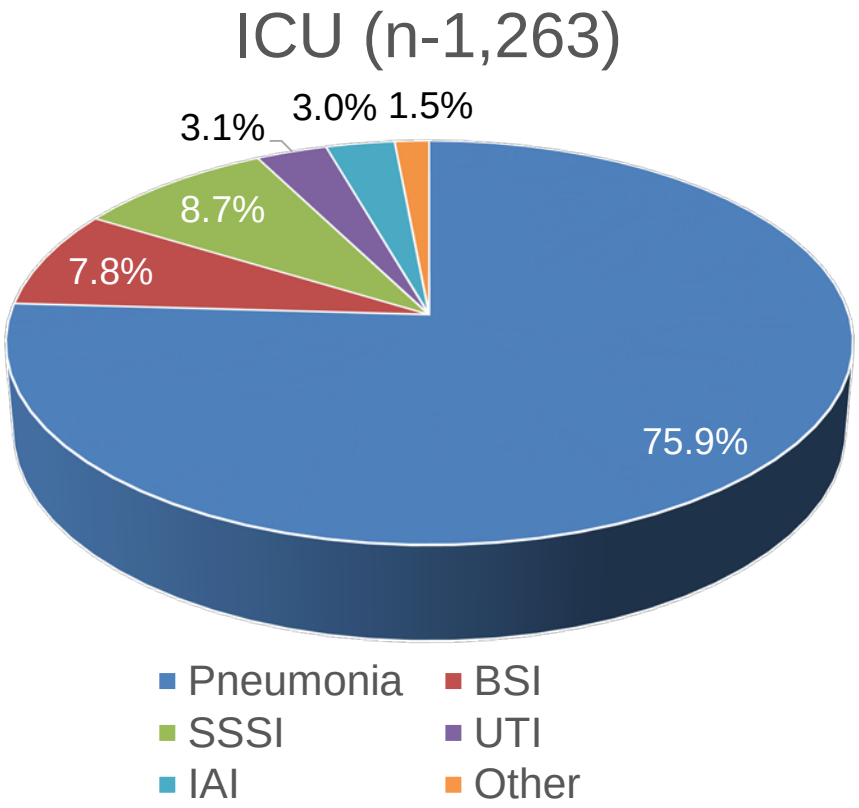
Susceptibility testing

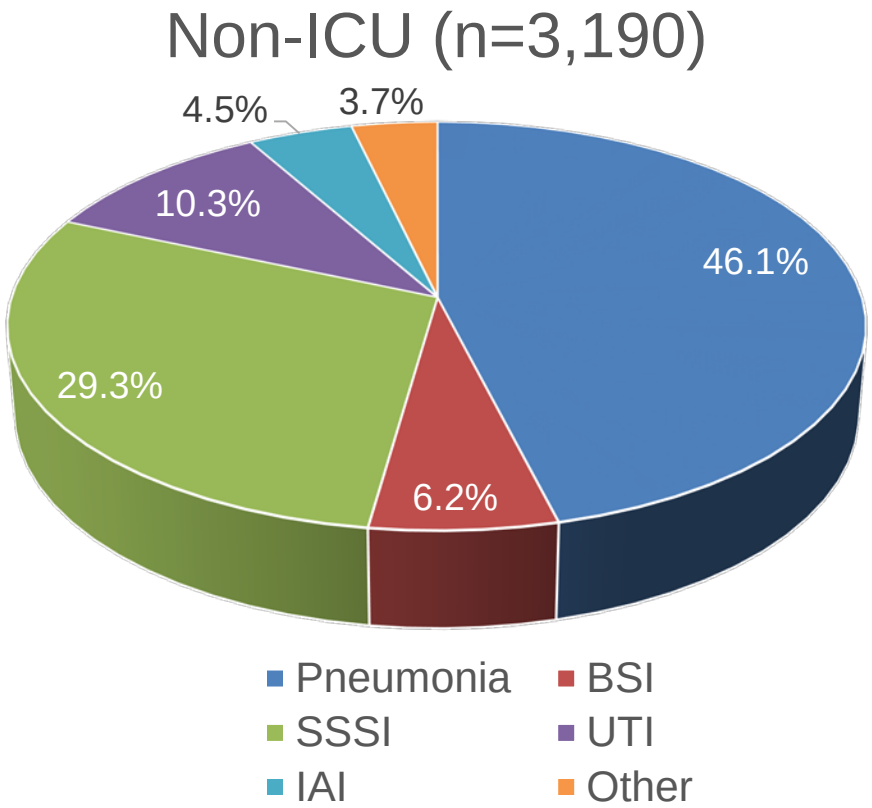
- Broth microdilution test methods by CLSI standards
- Ceftazidime-avibactam with avibactam at fixed concentration of 4 µg/mL
- US FDA breakpoint criteria applied for ceftazidime-avibactam when testing Enterobacteriaceae and *P. aeruginosa*
  - Susceptible at ≤8 µg/mL
  - Resistant at ≥16 µg/mL

Results

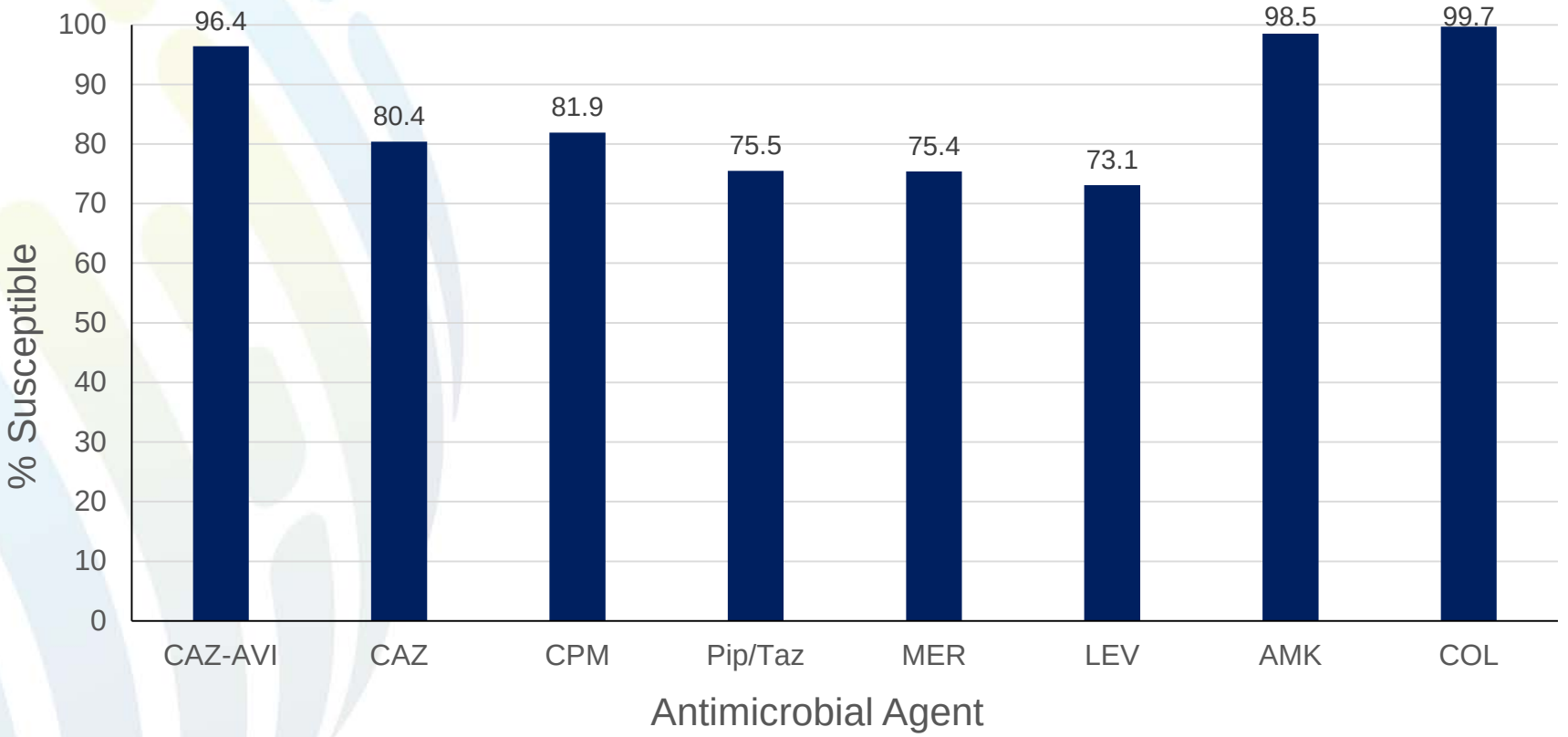
- Total of 4,453 isolates
  - 1,263 from ICU patients
  - 3,190 from non-ICU patients

Distribution of Organisms by Infection Type

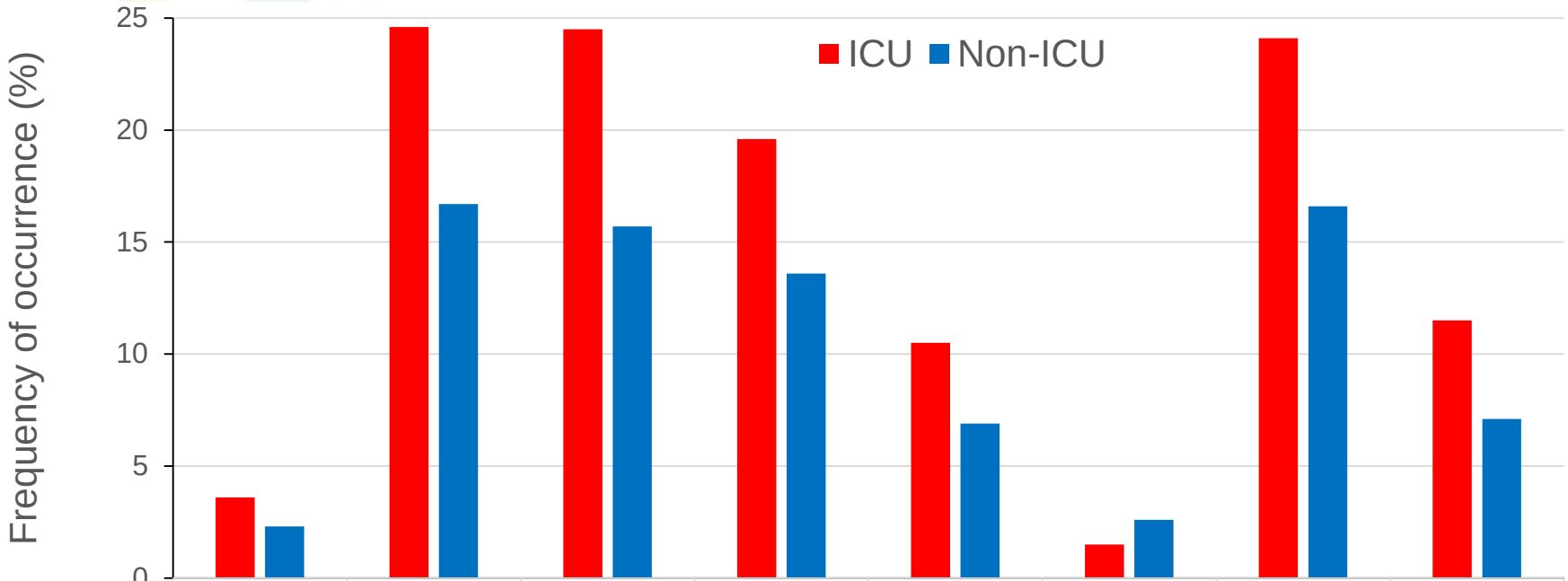




Antimicrobial Susceptibility of *P. aeruginosa* from ICU Patients

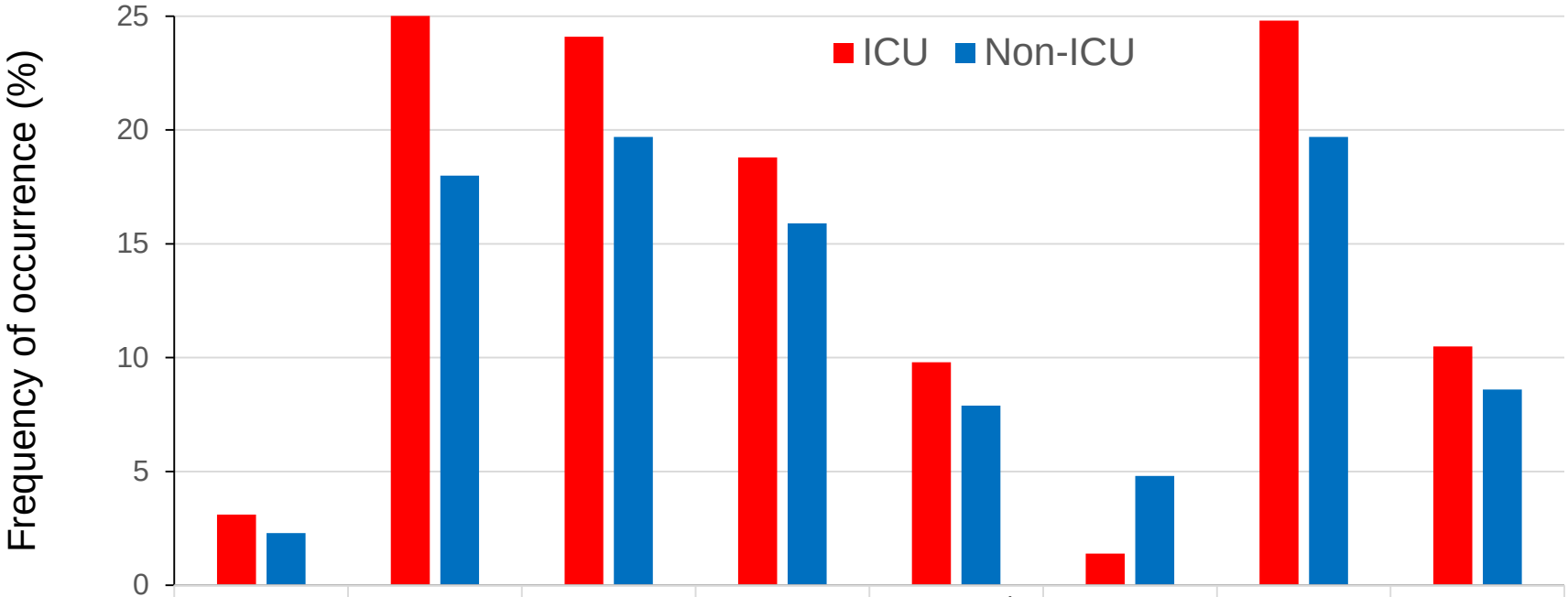


Antimicrobial Susceptibility (%NS) of *P. aeruginosa* from ICU and non-ICU Patients (all infection types)



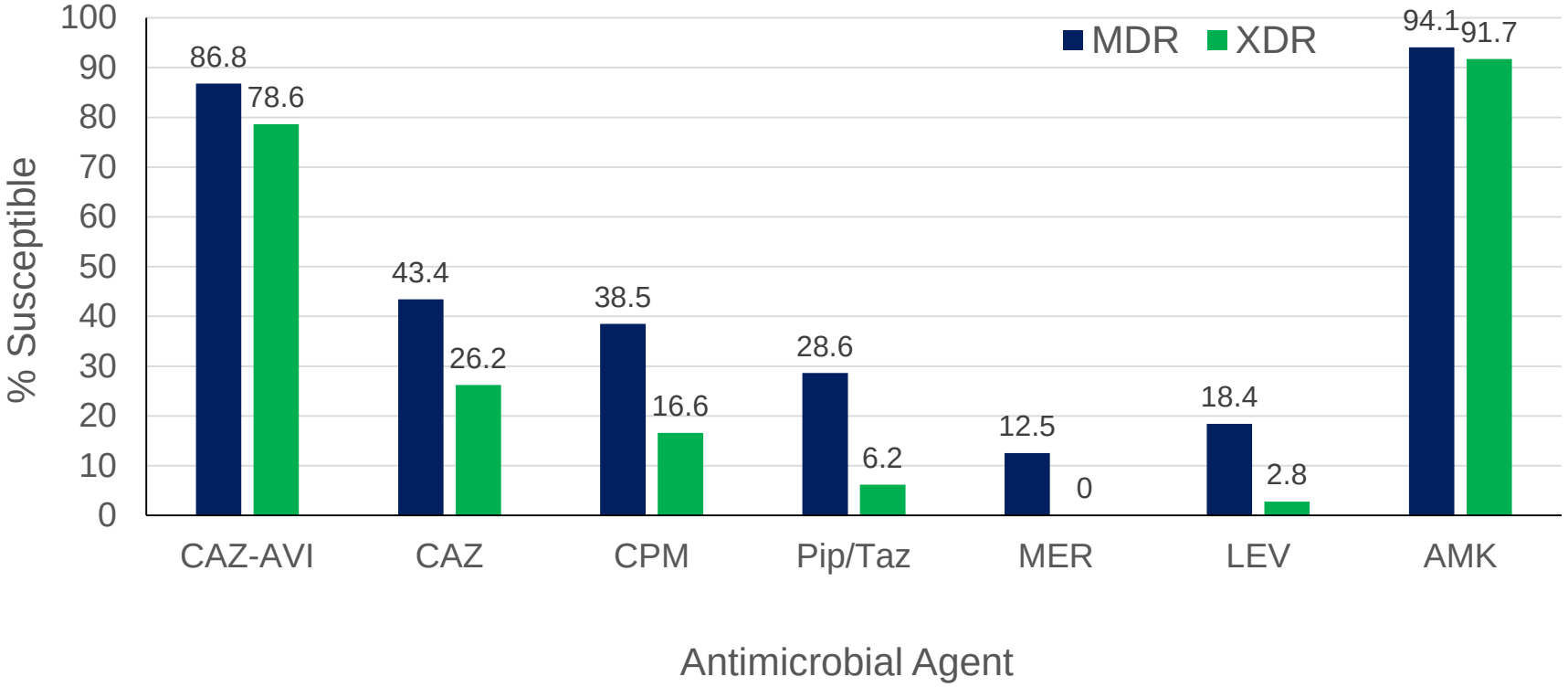
	CAZ-AVI-NS	MER-NS	P/T-NS	CAZ-NS	MER & P/T & CAZ-NS	AMK-NS	MDR	XDR
ICU	3.6	24.6	24.5	19.6	10.5	1.5	24.1	11.5
Non-ICU	2.3	16.7	15.7	13.6	6.9	2.6	16.6	7.1

Antimicrobial Susceptibility (%NS) of *P. aeruginosa* from Patients with Pneumonia (ICU vs. non-ICU)

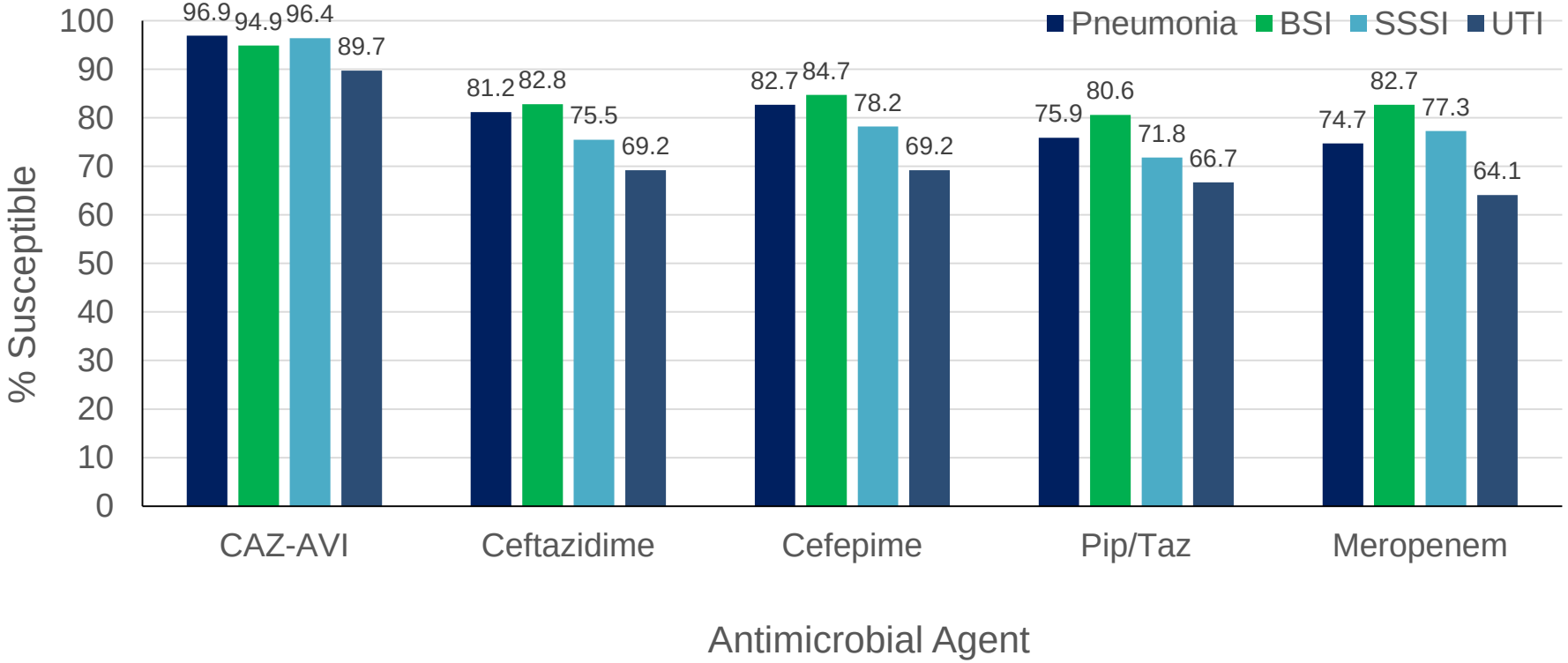


	CAZ-AVI-NS	MER-NS	P/T-NS	CAZ-NS	MER & P/T & CAZ-NS	AMK-NS	MDR	XDR
ICU	3.1	25.3	24.1	18.8	9.8	1.4	24.8	10.5
Non-ICU	2.3	18	19.7	15.9	7.9	4.8	19.7	8.6

Antimicrobial Susceptibility (%S) of MDR and XDR (all infections)



Antimicrobial Susceptibility of *P. aeruginosa* from ICU Patients Stratified by Infection Type



P. aeruginosa from ICU Patients: Cross-resistance Between β-lactams

Organism subset (n)	% Susceptible			
	Meropenem	Ceftazidime	Pip/Taz	CAZ-AVI
MER-NS (311)	--	55.0	41.2	87.8
CAZ-NS (247)	43.3	--	6.5	81.8
Pip/Taz-NS (309)	40.8	25.2	--	86.4
CAZ-AVI-NS (45)	15.6	0.0	6.7	--
MER & CAZ & PT-NS (133)	--	--	--	73.7

Conclusions

- Lower susceptibility rates were observed among ICU isolates compared with non-ICU isolates
- Ceftazidime-avibactam exhibited potent *in vitro* activity and spectrum when tested against a large collection of recent *P. aeruginosa* clinical isolates from ICU and non-ICU patients, including MDR and XDR strains

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