



Frequency of Occurrence and Antimicrobial Susceptibility of Bacteria from ICU Patients with Pneumonia

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Disclosure



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JMI Laboratories has received contracts and research grants in 2015-2016 from:

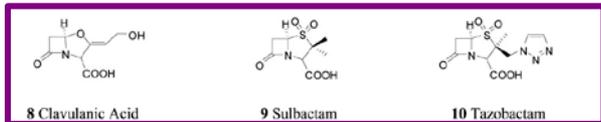
- Achaogen
- Actavis
- Actelion
- AmpliPhi
- Anacor
- Astellas
- AstraZeneca
- Basilea
- Bayer
- Cardeas
- Cellceutix
- CEM-102 Pharmaceuticals
- Cempra
- Cidara
- Cormedix
- Cubist
- Debiopharm
- Dipexium
- Dong Wha
- Durata
- Enteris
- Exela
- Forest
- Furiex
- Genentech
- Geom Therapeutics
- GSK
- Helperby
- Janssen
- Lannett
- Longitude
- Meiji Seika Kasha
- Melinta
- Merck
- Motif
- Nabriva
- Novartis
- Paratek
- Pfizer
- Pocared
- PTC Therapeutics
- Rempex
- Roche
- Salvat
- Scynexis
- Seachaid
- Shionogi
- Tetrphase
- The Medicines Co.
- Theravance
- VenatoRX
- Vertex
- Wockhardt
- Zavante
- Other corporations

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

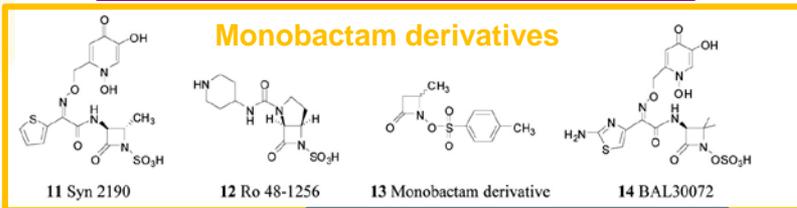
- Ceftazidime is a well described third-generation cephalosporin with broad-spectrum activity
- Avibactam (formerly NXL-104) is a member of a novel class of non- β -lactam β -lactamase inhibitors, the diazabicyclooctanes (DBOs)
- Avibactam can effectively inactivate:
 - Class A: ESBL and KPC
 - Class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

β-lactamase Inhibitors

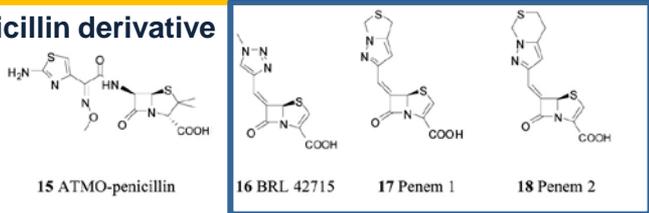
Clinically available



Monobactam derivatives

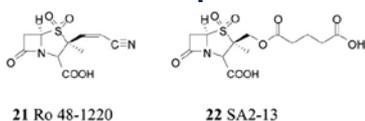
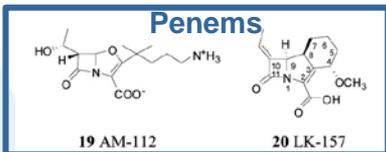


Penicillin derivative

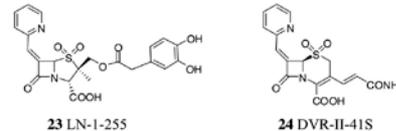


Penems

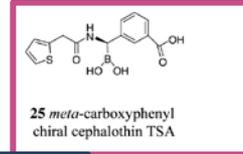
Penam Sulphones



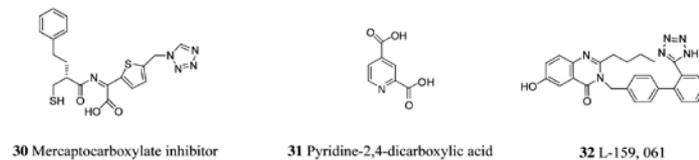
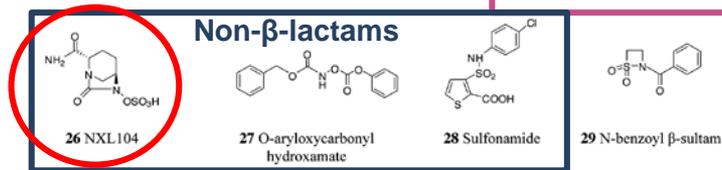
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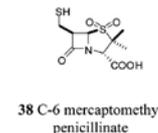
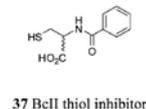
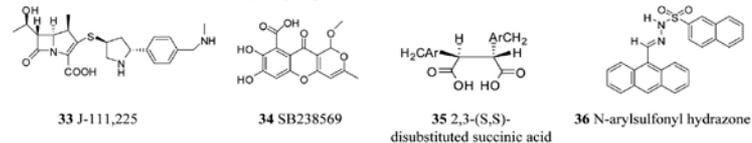
Boronic acid transition state analog



Non-β-lactams



MBL inhibitors



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



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

Spectrum of Activity of Avibactam



β-Lactamase		Clavulanate	Tazobactam	Avibactam
Class A	TEM, SHV and ESBLs	✓	✓	✓
	CTX-M and ESBLs	✓	✓	✓
	PER, VEB, GES	✓	✓	✓
	KPC	✗	✗	✓
Class B	IMP, VIM, NDM	✗	✗	✗
Class C	Chromosomal <i>Enterobacteriaceae</i> AmpC	✗	✗	✓
	Chromosomal <i>Pseudomonas</i> AmpC	✗	✗	✓
	Plasmidic ACC, DHA, FOX, LAT, MIX, MIR, ACT	✗	✗	✓
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 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 evaluate the frequency of occurrence of bacteria isolated from ICU patients with pneumonia, including VAP (2013-2015)
- To evaluate the antimicrobial activities of ceftazidime-avibactam (CAZ-AVI) and comparator agents against bacteria isolated from ICU patients with pneumonia (2013-2015)

Bacterial Isolates

- Collected in 2013-2015 as part of the International Network for Optimal Resistance Monitoring (INFORM) Program
- 65 medical centers among 37 states from all nine US Census divisions
- Consecutive collected bacterial isolates from lower respiratory tract sites determined to be significant by local criteria as the reported probable cause of pneumonia

Bacterial Isolates

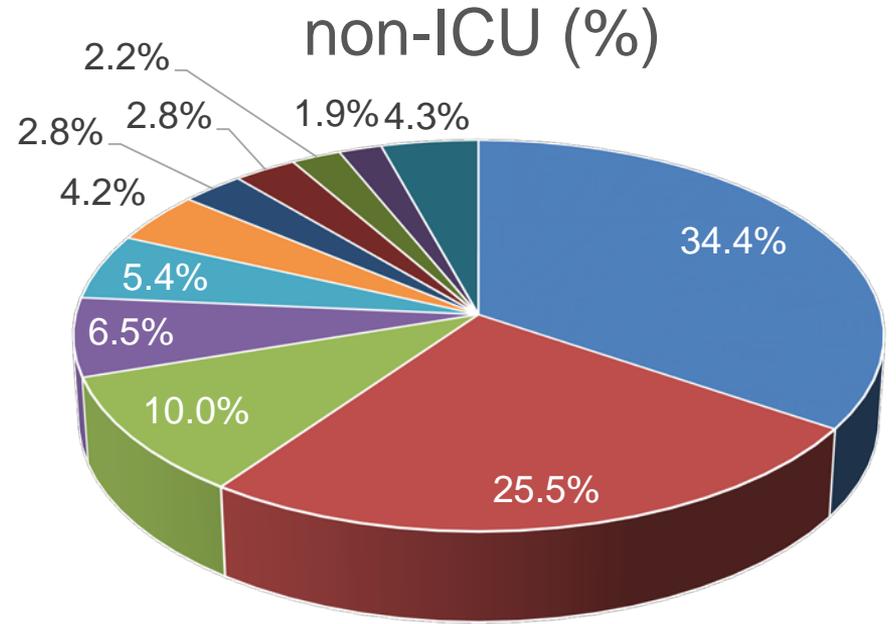
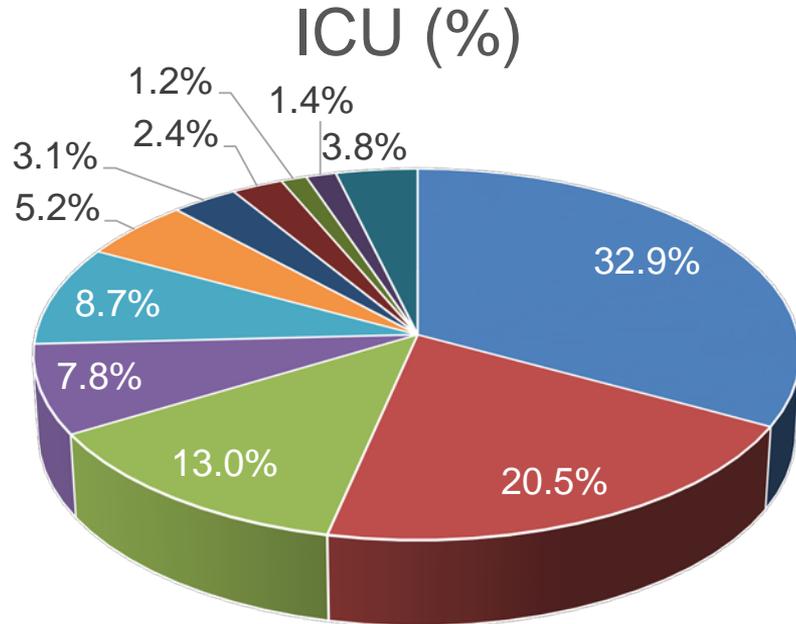
- Only isolates from invasive sampling (transtracheal aspiration, bronchoalveolar lavage, protected brush samples, qualified sputum samples, etc.) were accepted
- The frequency of occurrence of organisms was based on all organisms collected from patients hospitalized with pneumonia in the same participant medical centers
- Species identification was confirmed by standard biochemical tests and using the MALDI-TOF, where necessary

Susceptibility testing

- Broth microdilution test methods by CLSI standards
- Ceftazidime-avibactam with avibactam at fixed concentration of 4 $\mu\text{g}/\text{mL}$
- US FDA breakpoint criteria applied for ceftazidime-avibactam when testing Enterobacteriaceae and *P. aeruginosa*
 - Susceptible at $\leq 8 \mu\text{g}/\text{mL}$
 - Resistant at $\geq 16 \mu\text{g}/\text{mL}$

- A total of 9,179 isolates from patients with pneumonia
 - 3,632 from ICU patients, including 918 with VAP
- Among organisms from ICU patients
 - 63.7% Gram-negatives
 - 35.7% Gram positives (mainly *S. aureus* 32.9%)

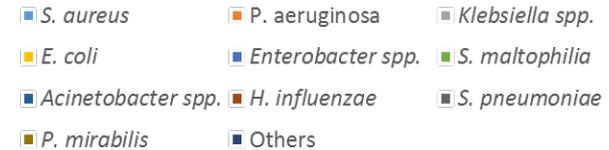
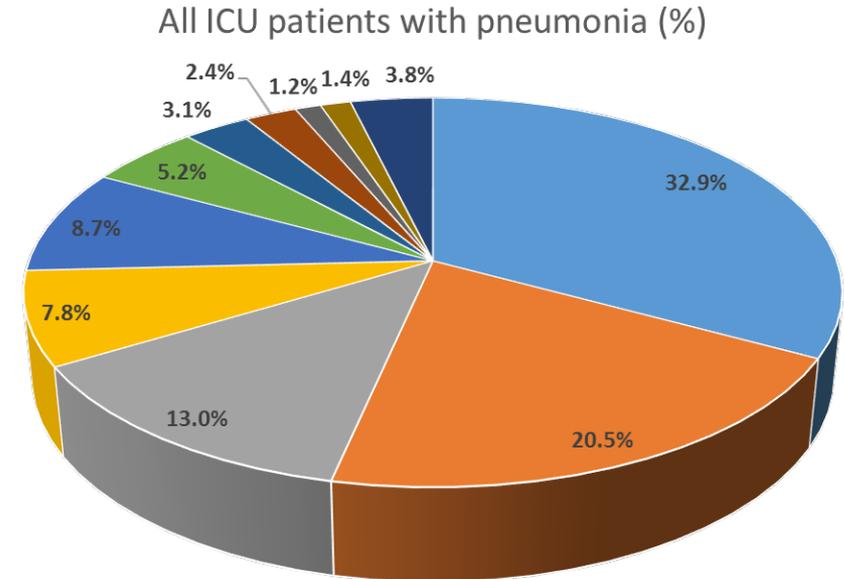
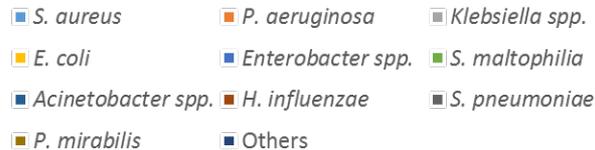
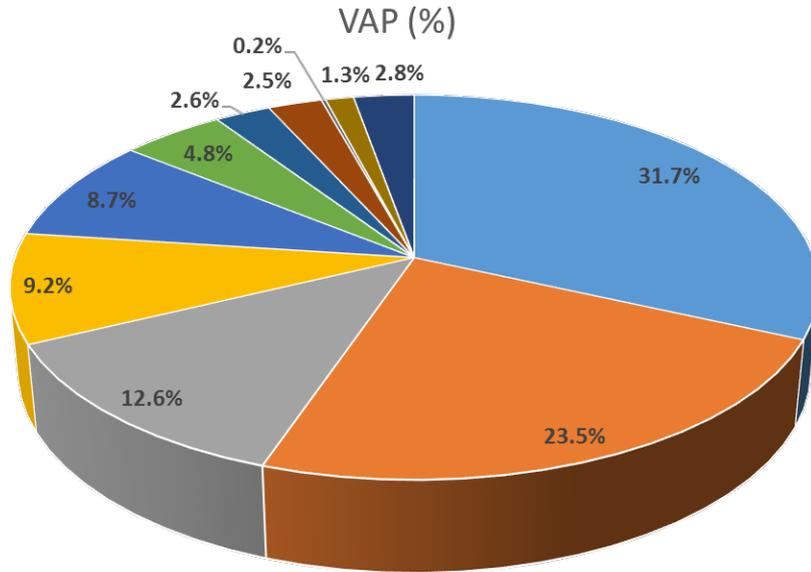
Frequency of Occurrence of Organisms Isolated from Patients with Pneumonia (ICU vs. non-ICU)



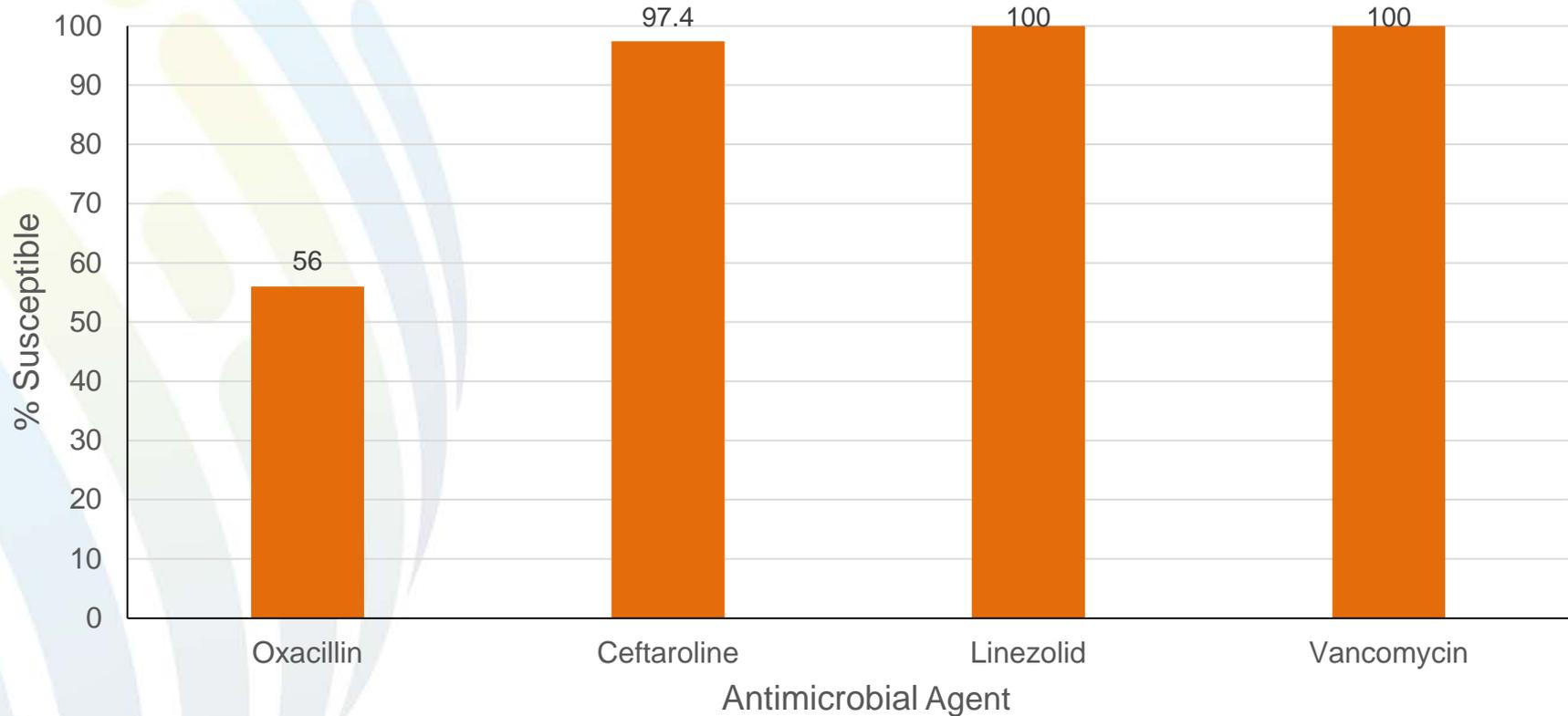
- *S. aureus*
- *E. coli*
- *Acinetobacter spp.*
- *P. mirabilis*
- *P. aeruginosa*
- *Enterobacter spp.*
- *S. maltophilia*
- *H. influenzae*
- *S. pneumoniae*
- Others

- *S. aureus*
- *E. coli*
- *Acinetobacter spp.*
- *P. mirabilis*
- *P. aeruginosa*
- *Enterobacter spp.*
- *S. maltophilia*
- *H. influenzae*
- *S. pneumoniae*
- Others

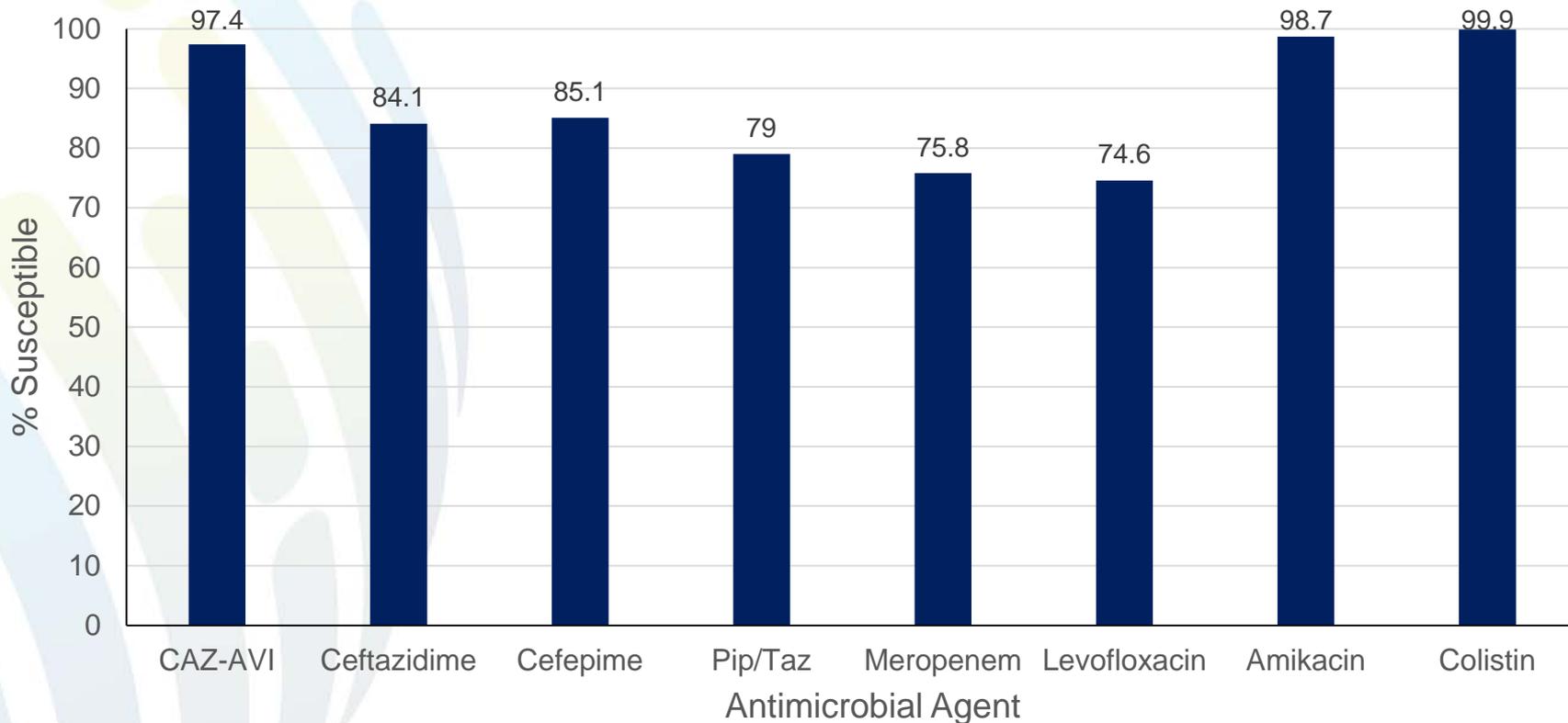
Frequency of Occurrence of Organisms Isolated from VAP



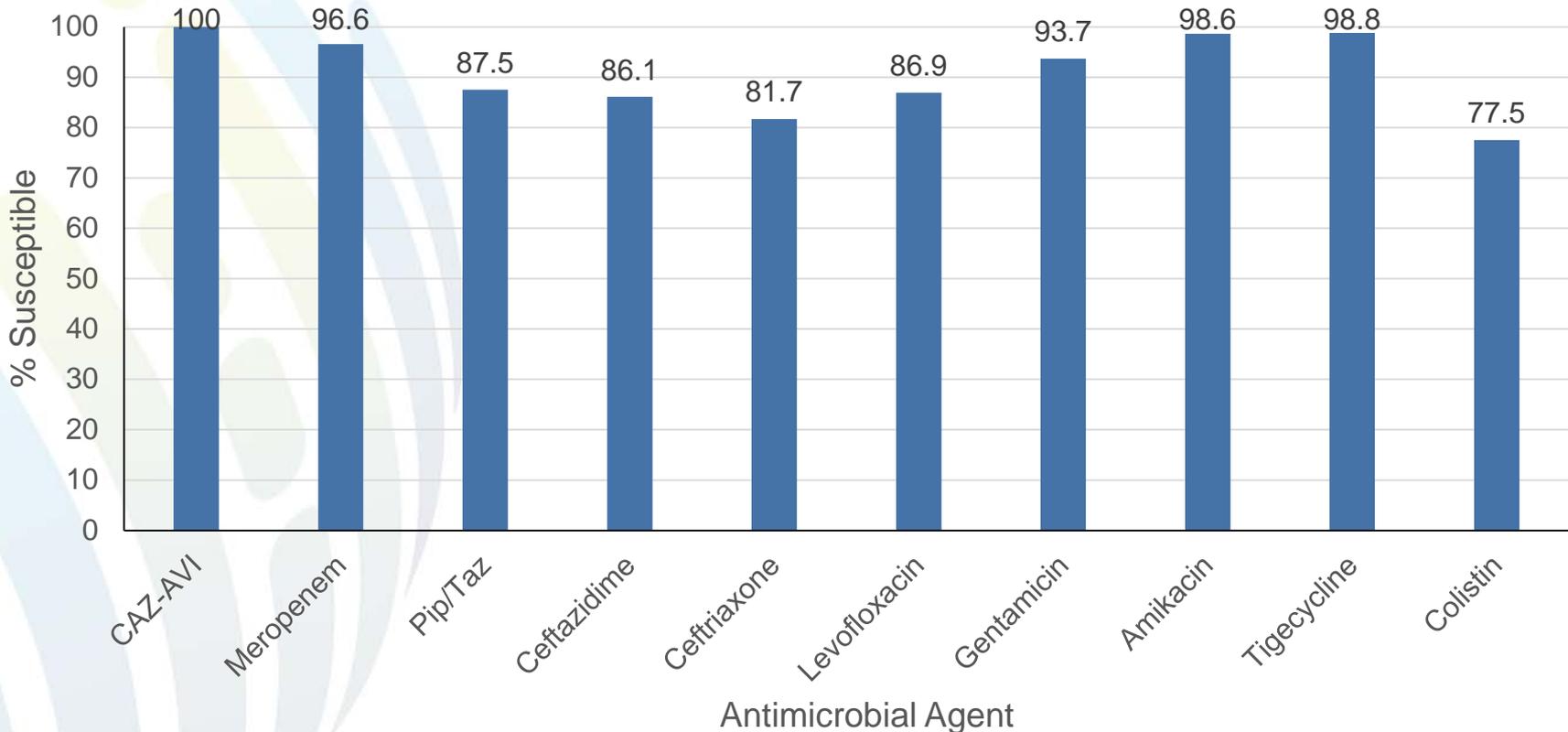
Antimicrobial Susceptibility of *S. aureus* from ICU Patients with Pneumonia (n=1,196)



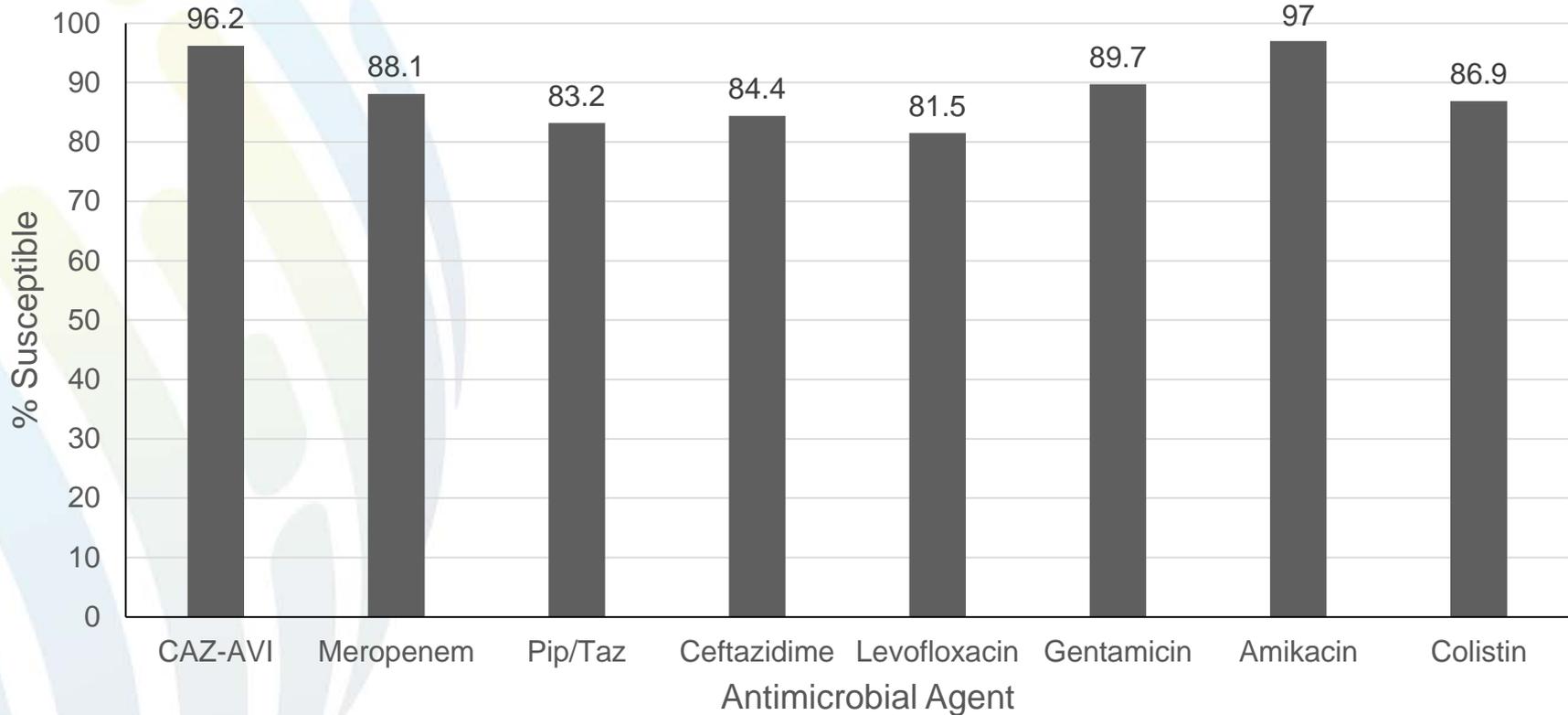
Antimicrobial Susceptibility of *P. aeruginosa* from Patients with Pneumonia (n=744)



Antimicrobial Susceptibility of Enterobacteriaceae from Patients with Pneumonia (n=1,365)



Overall Gram-negative Coverage (n=2,335)



Conclusions

- Two-thirds (65.3%) of organisms isolated from ICU patients with pneumonia were Gram-negatives
- High resistance rates were observed among Gram-positive and Gram-negative organisms isolated from ICU patients with pneumonia
- Ceftazidime-avibactam (96.2% overall coverage) and amikacin (97.0%) were the most active agents tested against Gram-negative organisms
- Meropenem and piperacillin/tazobactam were active against 88.1 and 83.1% of Gram-negative organisms overall
- Ceftazidime-avibactam represents a valuable treatment option for empiric antimicrobial therapy of pneumonia in ICU patients



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