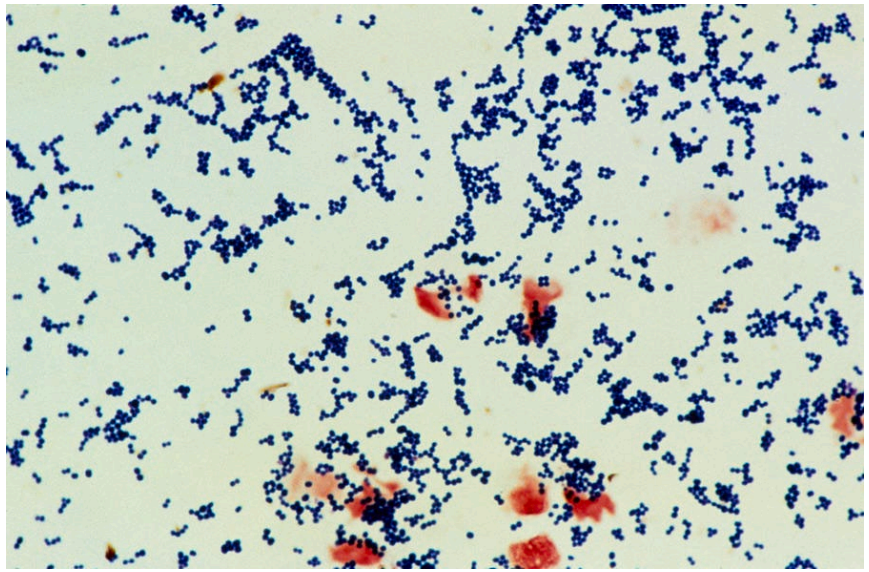
Clinical Impact of Vancomycin Minimum Inhibitory Concentration on Outcomes in Patients with Coagulase-Negative Staphylococcal Bacteremia

University Medical Center New Orleans
LCMC Health



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June 2nd, 2023

Abbreviations

CoNS	Coagulase-negative Staphylococci	**IDSA**	Infectious Diseases Society of America	**HTN**	Hypertension
BSI	Bloodstream infection	**IE**	Infective Endocarditis	**HLD**	Hyperlipidemia
CLSI	Clinical and Laboratory Standards Institute	**Echo**	Echocardiogram	**HCV**	Hepatitis C Virus
MIC	Minimum inhibitory concentration	**IV**	Intravenous	**HIV**	Human immunodeficiency virus
UMCNO	University Medical Center New Orleans	**TPN**	Total parenteral nutrition	**ID**	Infectious diseases
S	Susceptible	**ESRD**	End stage renal disease	**PICC**	Peripherally-inserted central catheter
I	Intermediate	**HD**	Hemodialysis	**IVDU**	Intravenous drug use
R	Resistant	**CHF**	Congestive hearth failure		
PBP	Penicillin Binding Protein	**COPD**	Chronic obstructive pulmonary disease		
MRSA	Methicillin-resistant *Staphylococcus aureus*	**EtOH**	Ethanol		

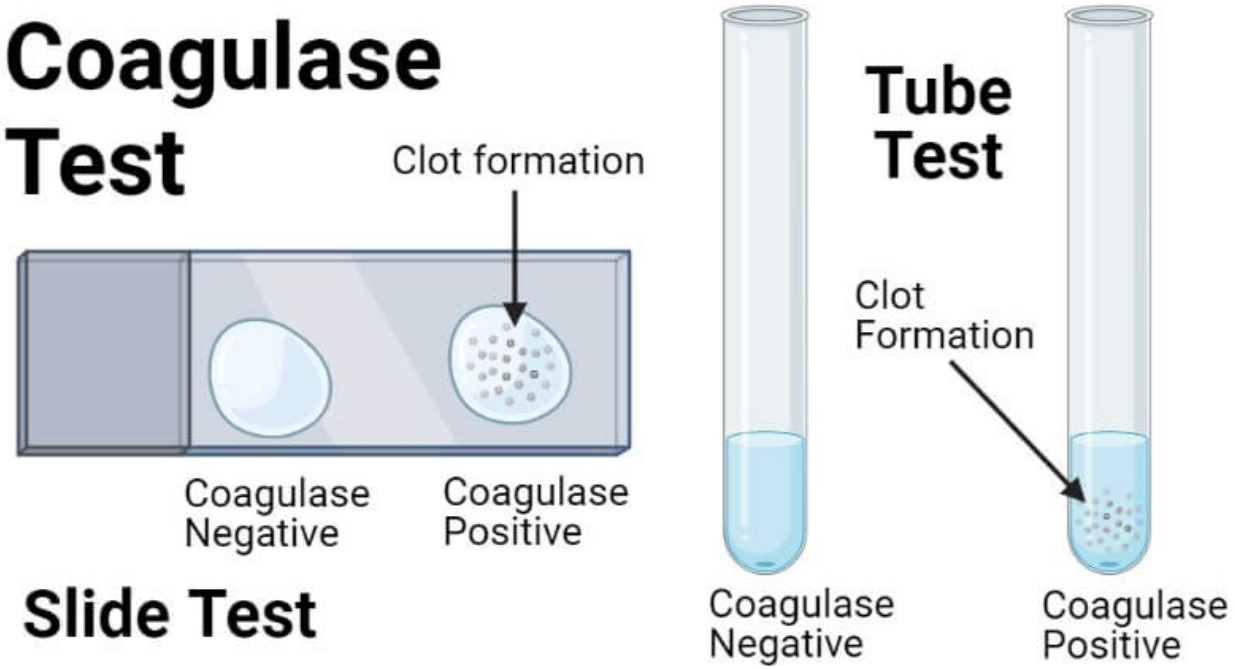
Objectives

- Describe the epidemiology of CoNS BSIs
- Summarize the microbiology of CoNS
- Recall the CLSI breakpoints for CoNS and compare them to *Staphylococcus aureus*
- Outline appropriate treatment for CoNS bloodstream infections
- Review study evaluating the clinical impact of vancomycin MICs of ≥2 mcg/mL in CoNS bacteremia

Background

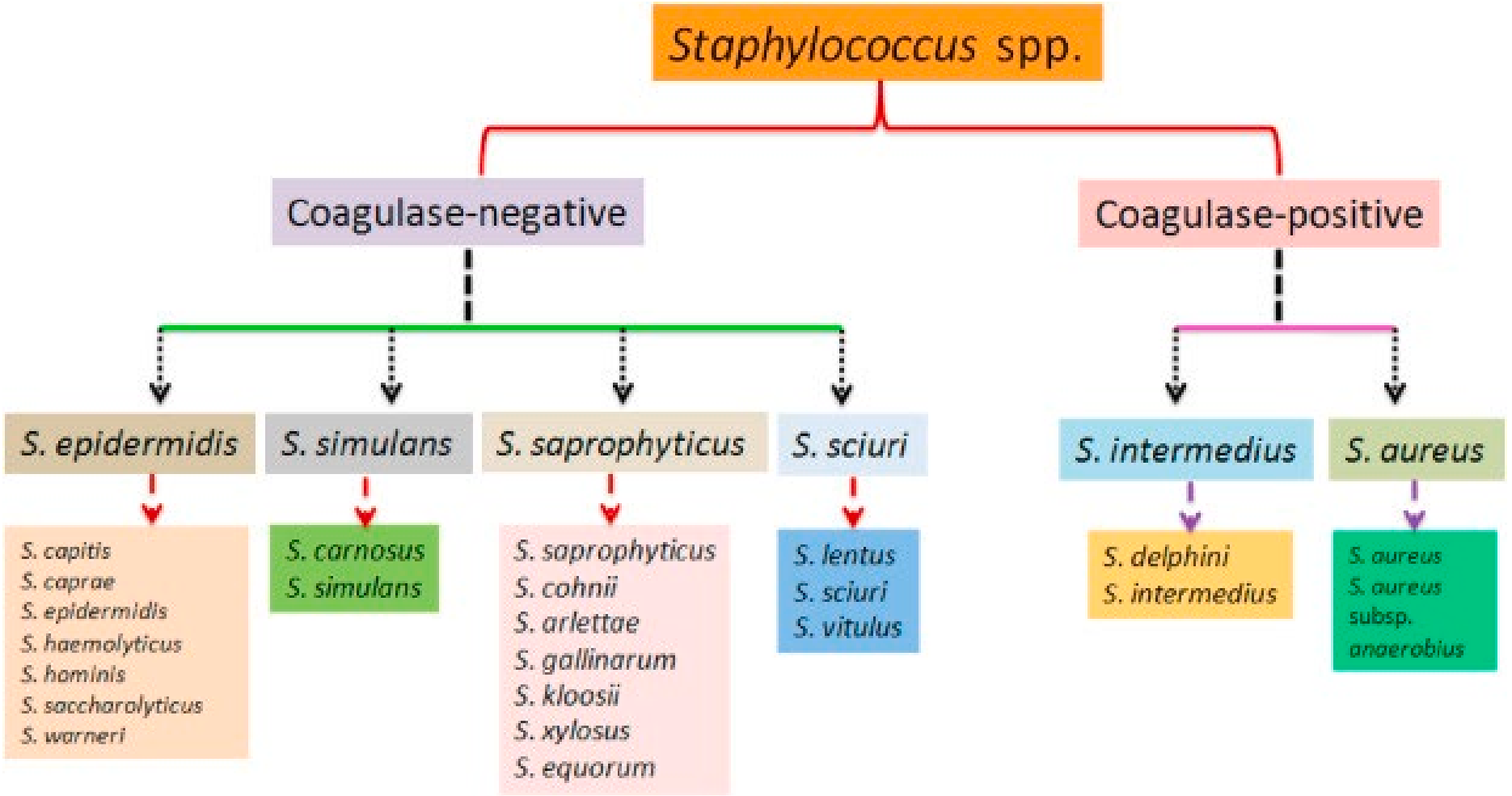
Background – CoNS

- Gram-positive organisms that are a common component of skin flora
- Heterogenous group of Staphylococci
- Laboratory testing performed to determine if coagulase positive or coagulase negative
- Differentiates *S. aureus* from other staphylococcal species
- CoNS are generally less virulent than *S. aureus*



Becker K, et al. *Clin Microbiol Rev*. 2014;27(4):870-926. doi:10.1128/CMR.00109-13
Aryal S. Microbe Notes. Available at https://microbenotes.com/coagulase-test-principle-procedure-and-result-interpretation/

Species of CoNS



https://www.sciencedirect.com/science/article/abs/pii/S0740002022000521

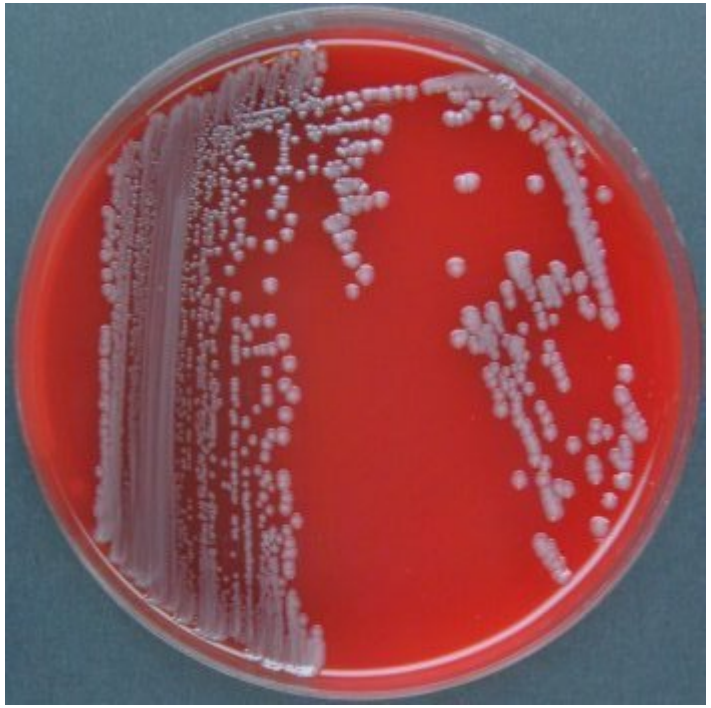
Epidemiology of CoNS

- Most common cause of nosocomial bacteremia
- Many of these bloodstream infections are secondary to intravenous catheter infection
- *S. epidermidis* is the most commonly isolated species of clinical significance
- CoNS readily adhere to foreign materials and form biofilms
- Determination of contamination versus true infection must be made

Richards Mjet al. *Crit Care Med*. 1999;27(5):887-892. doi:10.1097/00003246-199905000-00020
Wisplinghoff H, et al. *Clin Infect Dis*. 2004;39(3):309-317. doi:10.1086/421946
Pfaller Maet al. *Clin Microbiol Rev*. 1988;1(3):281-299. doi:10.1128/CMR.1.3.281

Infection versus Contamination

- Since CoNS are normal skin flora, there is risk for contamination of collected isolates
- Up to 65% of isolated CoNS from blood cultures may be contaminants
- This can occur during various steps of culture processing
- Assessment of the clinical significance of the positive blood culture must be performed



https://atlas.sund.ku.dk/microatlas/food/bacteria/Staphylococcus_epidermidis/

Elzi L, et al. *Clin Microbiol Infect*. 2012;18(9):E355-E361. doi:10.1111/j.1469-0691.2012.03964.x

Infection versus Contamination

Number of positive bottles and the number of cultures obtained

Species of CoNS recovered

Length of time for blood cultures to become positive

Culture collection site

Clinical signs of infection

Magadia RR, et al. *Infect Dis Clin North Am*. 2001;15(4):1009-1024. doi:10.1016/s0891-5520(05)70184-7
Mirrett S, et al. *J Clin Microbiol*. 2001;39(9):3279-3281. doi:10.1128/JCM.39.9.3279-3281.2001
Weinstein MP. *Clin Infect Dis*. 1996;23(1):40-46. doi:10.1093/clinids/23.1.40

CoNS Blood Culture Reporting at UMCNO

All CoNS isolated from blood cultures are speciated for laboratory recording purposes

- Species can be seen by microbiology lab

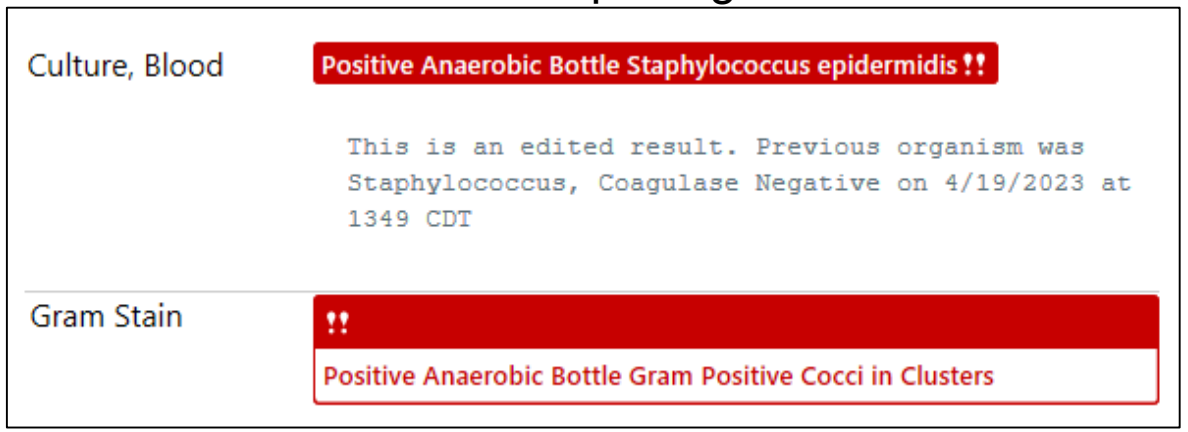
Species is only released to the EMR under certain circumstances:

- Growth from more than 1 set of blood cultures AND
- CoNS species must be the same in both sets AND
- Susceptibilities of the CoNS must be the same for both sets

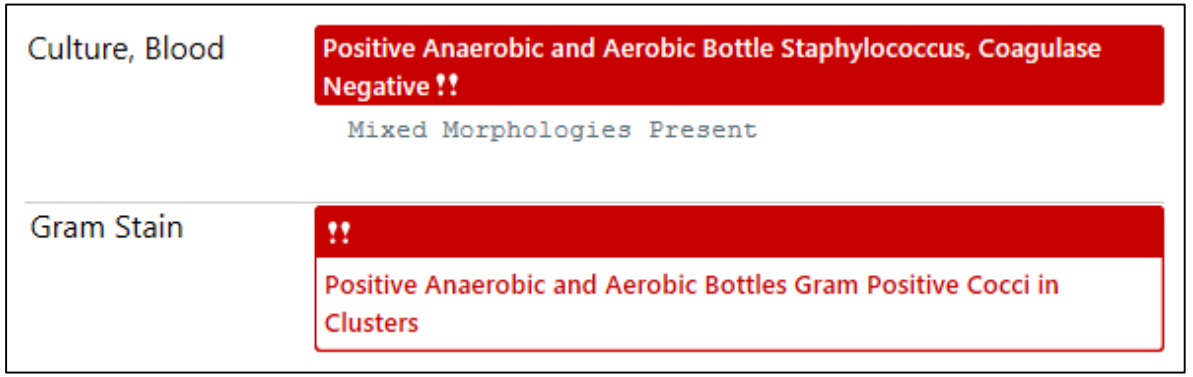
If these conditions are not met, the isolate(s) are deemed contaminants and reported only as CoNS

- Unless requested by physician

Possible pathogen



Probable contaminant



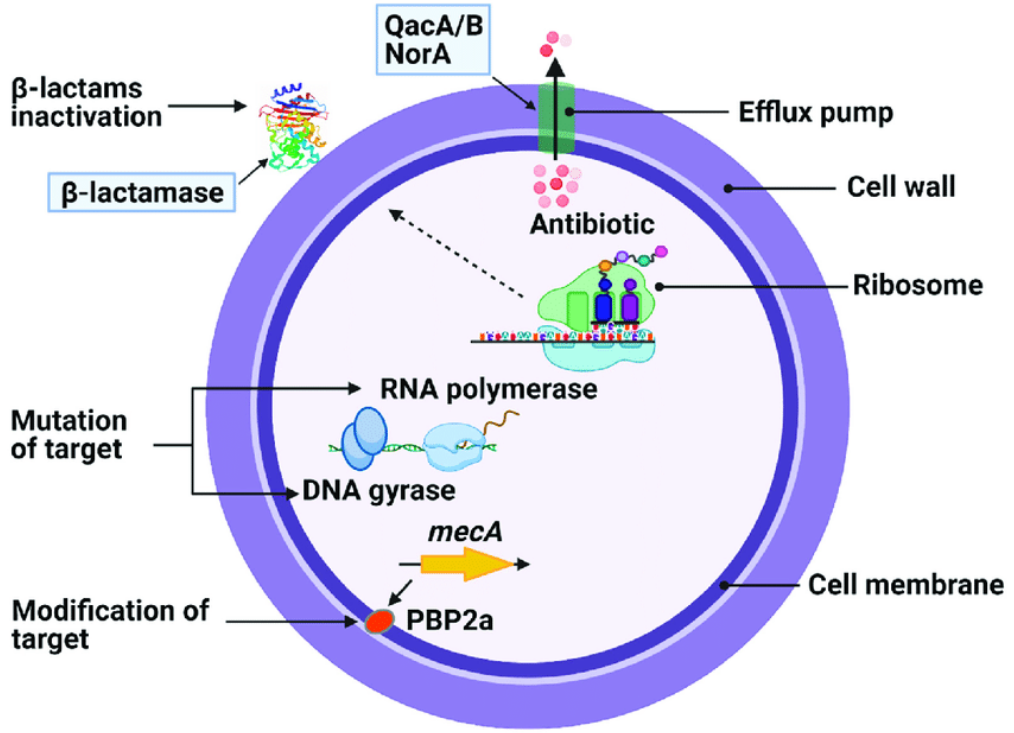
CoNS Breakpoints

MIC Breakpoints for CoNS				
Antibiotic	**Species**	**S**	**I**	**R**
Oxacillin	*S. lugdunensis*	≤ 2 mcg/mL	-	≥ 4 mcg/mL
	All CoNS except *S. lugdunensis*	≤ 0.5 mcg/mL	-	≥ 1 mcg/mL
Vancomycin	All CoNS	≤ 4 mcg/mL	8 – 16 mcg/mL	≥ 32 mcg/mL
	S. aureus	≤ 2 mcg/mL	4 – 8 mcg/mL	≥ 16 mcg/mL

Lewis J, Weinstein M, et al. CLSI M100-ED32:2022 Performance Standards for Antimicrobial Susceptibility Testing, 32nd Edition. Published February 2022.

CoNS Resistance Trends

- About 80% of CoNS species are methicillin-resistant
  - Presence of the mecA gene which causes mutations in PBP-2A
  - Confers resistance to antistaphylococcal penicillins and most beta-lactam antibiotics
- Vancomycin heteroresistance has also been described in CoNS
  - Possibly due to increased cell wall thickness
  - Similar mechanism of resistance to *S. aureus* although less common



https://www.researchgate.net/figure/Molecular-mechanisms-of-antibiotic-resistance-in-Staphylococcus-aureus-Antimicrobial_fig1_350713416

Diekema DJ, et al. *Clin Infect Dis*. 2001;32 Suppl 2:S114-S132. doi:10.1086/320184
Ryffel C, et al. *Gene*. 1990;94(1):137-138. doi:10.1016/0378-1119(90)90481-6

Effect of Vancomycin MIC on MRSA

- A vancomycin MIC of ≥2 mcg/mL for MRSA has been associated with increased clinical failure and mortality

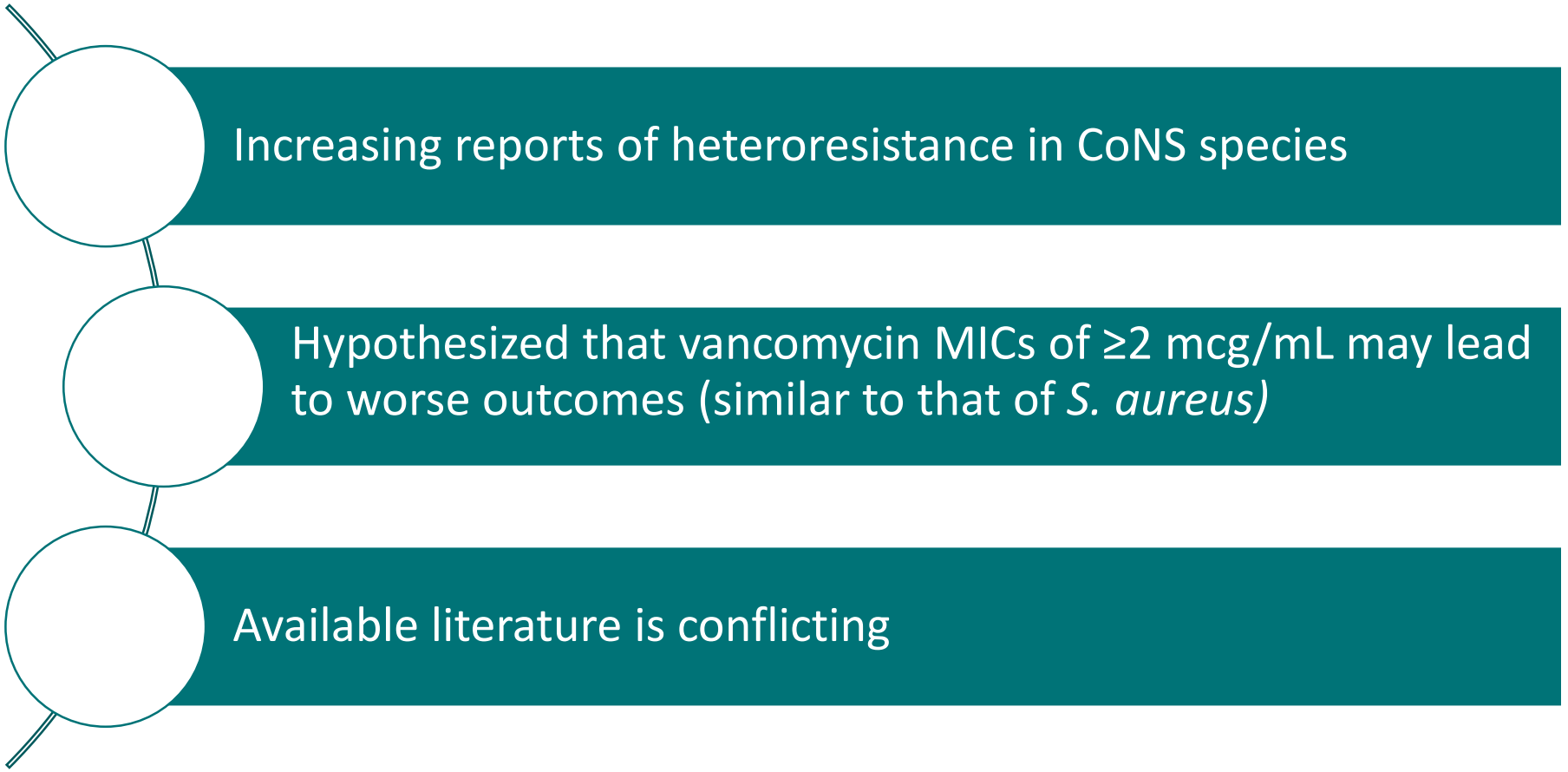
- IDSA guidelines recommend using an alternative agent in treatment of MRSA with a vancomycin MIC of ≥2 mcg/mL

Study	Design	Findings

Soriano A, et al	• Prospective follow-up study
	  • 414 episodes of MRSA bacteremia from 1991 through 2005
	• Stratified into groups
	  • One being receipt of empiric vancomycin and a vancomycin MIC of 2 µg/mL (n=40)
		• Vancomycin MIC of 2 µg/mL and treatment with vancomycin associated with:
		  • Lower risk of shock (OR, 0.33; 95% CI, 0.15–0.75)
		  • Higher risk of mortality (OR, 6.39; 95% CI, 1.68–24.3)

Rybak MJ, et al. *Am J Health Syst Pharm*. 2020;77(11):835-864. doi:10.1093/ajhp/zxaa036
Soriano Aet al. *Clin Infect Dis*. 2008;46(2):193-200. doi:10.1086/524667

Vancomycin Heteroresistance in CoNS



Mashaly GE, et al. *Ann Clin Microbiol Antimicrob.* 2017;16(1):63. doi:10.1186/s12941-017-0238-5
García de la Mària C, et al. *PLoS One*. 2015;10(5):e0125818. doi:10.1371/journal.pone.0125818

Vancomycin Heteroresistance in CoNS

Study	Design	Results
Mashaly GE, et al.	• Prospective in-vitro study of 58 blood samples positive for CoNS • Isolates screened for vancomycin heteroresistance on agar containing 4 µg/mL vancomycin	• 75.9% of isolates oxacillin resistant • All had susceptible vancomycin MICs • 15.5% (9/58) could grow on agar containing 4 µg/mL of vancomycin
García de la Mària C, et al.	• Prospective cohort study including 88 blood culture CoNS isolates of patients with IE • 98 isolates were available for the 88 included patients	• 71% (70/98) of isolates were *S. epidermidis* • 44 were methicillin-resistant (51% of *S. epidermidis*) • 42 had a vancomycin MIC ≥2 µg/mL (20 treated with vancomycin) • Highest one-year mortality in vancomycin-treated patients with vancomycin MICs ≥2 µg/mL (48% MIC <2 mcg/mL, 65% MICs ≥2, *P* = 0.003)

Mashaly GE, et al. *Ann Clin Microbiol Antimicrob*. 2017;16(1):63. doi:10.1186/s12941-017-0238-5
García de la Mària C, et al. *PLoS One*. 2015;10(5):e0125818. doi:10.1371/journal.pone.0125818

Appropriate Therapy for CoNS Bacteremia

- Currently, vancomycin is the empiric drug of choice for CoNS bacteremia due to high incidence of methicillin-resistance
- Tailored antibiotic selection should be guided by susceptibility results
- Duration of therapy is dependent on likelihood of contamination, source of infection, and complicating factors

Categories of CoNS Bacteremia

Simple (treat for 0-3 days)

- Single blood culture positive for CoNS
- Negative follow-up blood culture
- No signs or symptoms of local infection at catheter site
- No signs or symptoms of metastatic infection
- No indwelling IV prosthetic devices

Uncomplicated (treat for 5-7 days)

- Two or more blood cultures positive for CoNS drawn 24 hours apart or less
- Single blood culture positive for CoNS with signs or symptoms of infection at catheter site

Complicated (treat for 7-28 days or longer)

- Echo with evidence of endocarditis
- Signs or symptoms of metastatic infection

Holland Tlet al. *JAMA*. 2018;320(12):1249-1258. doi:10.1001/jama.2018.13155

Appropriate Therapy for CoNS Bacteremia

Study	Design	Results

Holland TL, et al.	• Randomized clinical trial
	• 509 adults with staphylococcal bacteremia
	  • 385 (76%) with CoNS bacteremia
	  • 116 (23%) with *S. aureus bacteremia*
	• Algorithm-based therapy (n = 255) or usual practice (n = 254)
	• Patient with complicated bacteremia were excluded
	  • 34 patients with complicated CoNS bacteremia identified after enrolled
		• No difference in clinical success
		  • 85.6% (166/194) of algorithm-based therapy
		  • 88% (168/191) of usual practice
		  • (−2.4 (−9.2 to ∞))
		• No difference in clinical success in complicated CoNS bacteremia
		  • 89.5% (17/19) of algorithm-based therapy
		  • 73.3% (11/15) of usual practice
		  • (16.1 (−10.2 to ∞))

Holland Tlet al. *JAMA*. 2018;320(12):1249-1258. doi:10.1001/jama.2018.13155

Study Objectives

Study Objectives

- The purpose of this study is to assess the clinical impact of CoNS BSIs with a vancomycin of MIC ≥2 µg/mL versus <2 mcg/mL

Methods

Methods

Design

- Retrospective cohort analysis

Data Collection

- A list of patients with a blood culture positive for CoNS provided by the UMCNO microbiology lab
- Included patients admitted between January 1, 2020, and August 1, 2022
- Served as the study population

Outcome Measures

Primary Outcome

- Difference in 30-day mortality between groups

Secondary Outcomes

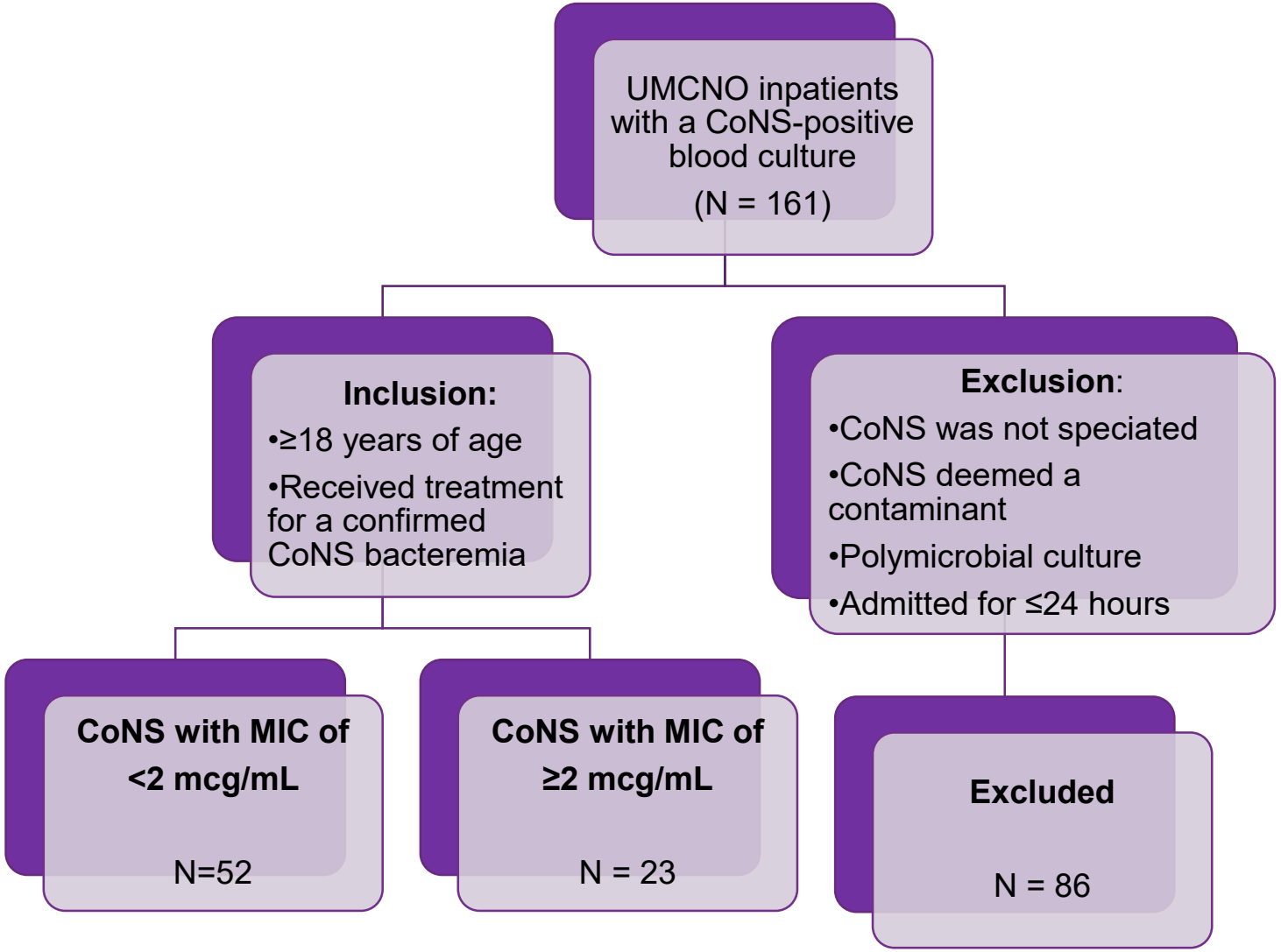
- Difference in in-hospital, all-cause mortality
- Difference in duration of bacteremia
- Difference in hospital length of stay
- Percentage of methicillin-resistant CoNS

Statistical Analyses

- Statistical analyses performed using Graphpad Prism and Statistics Kingdom
- A descriptive analysis was performed for baseline characteristics, primary, and secondary outcomes
- Categorical variables were described as percentages and frequency
  - Compared using Fischer exact test
- Continuous variables were described as medians and IQR
  - Compared using Mann-Whitney U test
- Groups were compared using a 2-sided P value with a value of ≤0.05 being statistically significant

Results

Patient Population



Baseline Characteristics

- Baseline characteristics similar between groups
- 56% (42/75) patients were male
- 52% (39/75) were black
- 35.7% (26/75) were white

Demographics	MIC <2 mcg/mL (n=52)	MIC ≥2 mcg/mL (n=23)	P value
Median age, years	53.3	51.3	0.48
Median weight, kg	80.7	77.1	0.15
Male, n (%)	33 (63.5)	9 (39.1)	0.08
Race/Ethnicity, n (%)			
Black	24 (46.1)	15 (65.3)	0.14
White	21 (40.4)	5 (21.7)	0.19
Other	7 (13.5)	3 (13)	1

Baseline Characteristics

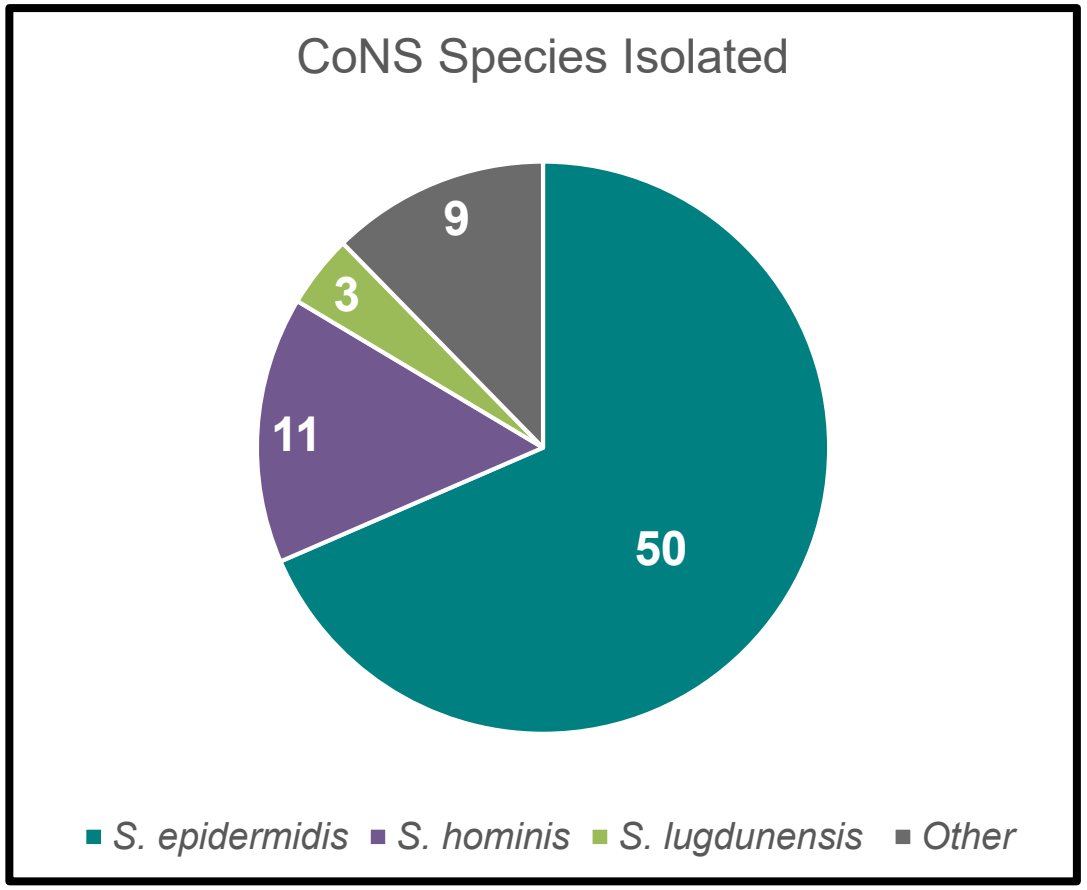
- History of chronic illness similar between groups

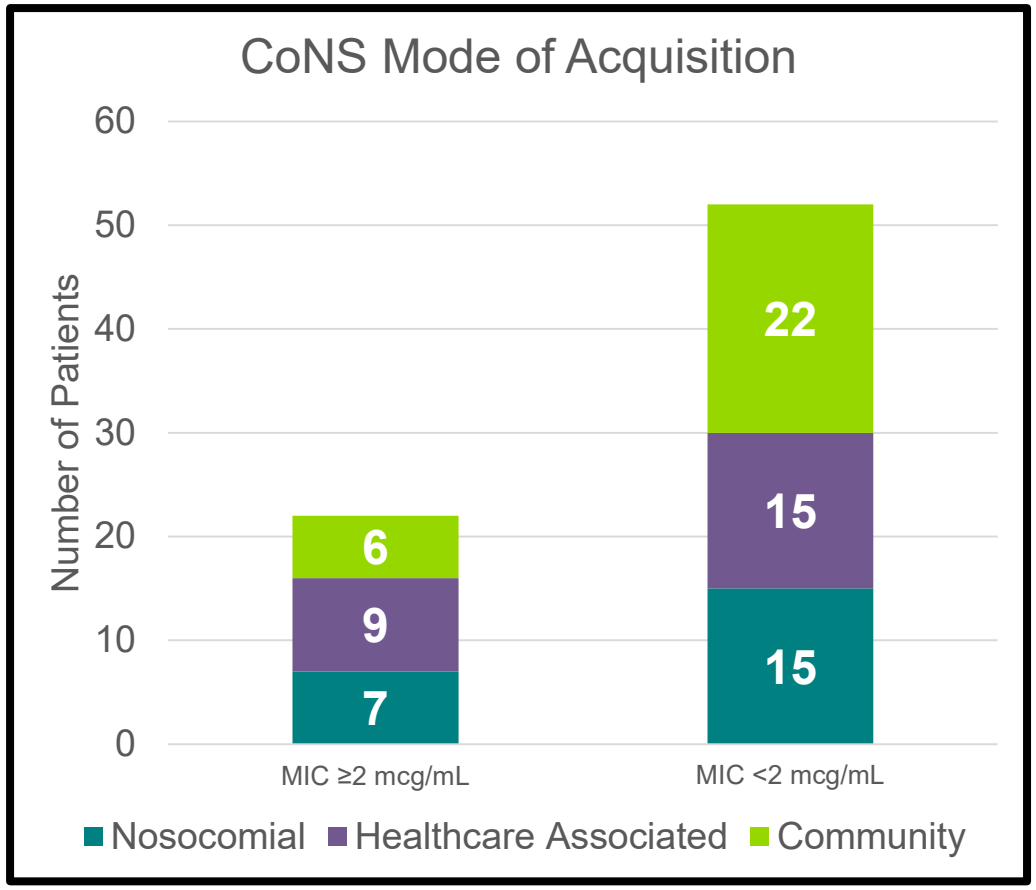
Demographics	MIC <2 mcg/mL (n=52)	MIC ≥2 mcg/mL (n=23)	P value
History of chronic illness			
Chronic decubitus ulcer	3 (5.8%)	1 (4.3%)	1
Obesity	2 (3.8%)	1 (4.3%)	1
Diabetes mellitus	11 (21.2%)	3 (13.0%)	0.53
IV Drug Use	7 (13.5%)	0 (0%)	0.09
Chronically TPN dependent	2 (3.8%)	2 (8.7%)	0.58
ESRD requiring HD	1 (1.9%)	2 (8.7%)	0.22
Malignancy	4 (7.7%)	3 (13.0%)	0.67
CHF	1 (1.9%)	1 (4.3%)	1
COPD	1 (1.9%)	0 (0%)	0.52
EtOH abuse	3 (5.8%)	0 (0%)	0.55
Paraplegia	3 (5.8%)	0 (0%)	0.55
Cirrhosis	1 (1.9%)	0 (0%)	1
HTN	1 (1.9%)	0 (0%)	1
HLD	1 (1.9%)	0 (0%)	1
HCV	3 (5.8%)	0 (0%)	0.55
HIV	1 (1.9%)	0 (0%)	1
Heart valve replacement	0 (0%)	2 (8.7%)	0.09

Baseline and Microbiologic Characteristics

Demographic	MIC <2 mcg/mL (n=52)	MIC ≥2 mcg/mL (n=23)	P value
ID consult, n (%)	35 (67.3)	19 (82.6)	0.27
Pitt bacteremia score, median	0	0	0.78 IQR (0, 1)
CoNS species, n (%)			
S epidermidis	30 (57.7)	20 (87)	0.02
S hominis	11 (21.2%)	1 (4.3)	0.09
S lugdunensis	3 (5.8)	1 (4.3)	0.55
Other CoNS spp.	8 (15.4)	1 (4.3)	0.26
Oxacillin resistance, n (%)	26 (50)	18 (78.3)	0.02

Microbiologic Characteristics





CoNS Acquisition Characteristics

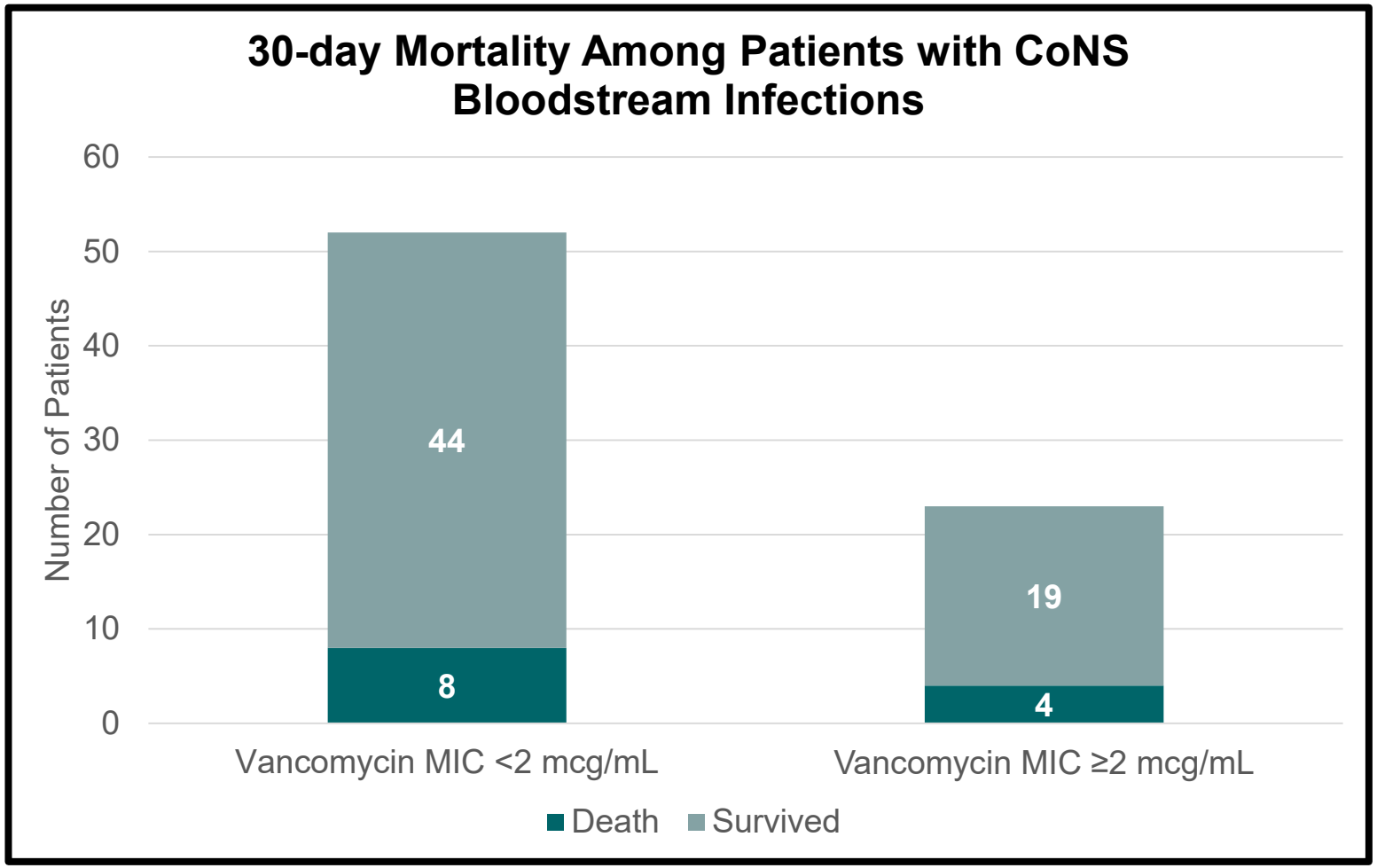
- Mode of acquisition was similar between groups
  - Community-acquired: 37.3% (28/75)
  - Non-nosocomial healthcare-associated: 32% (24/75)
  - Nosocomial acquisition: 29.3 % (22/75)
  - Unknown: 1.3% (1/75)

Demographic	CoNS with vancomycin MIC <2 mcg/mL (n=52)	CoNS with vancomycin MIC ≥2 mcg/mL (n=23)	P value
Mode of acquisition, n (%)			
Nosocomial	15 (28.8)	7 (30.4)	1
Non-nosocomial healthcare associated	15 (28.8)	9 (39.1)	0.43
Community	22 (42.3)	6 (26.1)	0.21
Unknown	0 (0)	1 (4.3)	0.31

CoNS Acquisition Characteristics

Demographic	Vancomycin MIC <2 mcg/mL (n=52)	Vancomycin MIC ≥2 mcg/mL (n=23)	P value
Source of CoNS, n (%)			
TPN line	5 (9.6%)	5 (21.7%)	0.56
PICC line	10 (19.2%)	4 (17.4%)	0.27
Midline	4 (7.7%)	1 (4.3%)	1
Skin	10 (19.2%)	4 (17.4%)	1
Oral	1 (1.9%)	0 (0%)	1
Pacemaker	0 (0%)	1 (4.3%)	1
IVDU	2 (3.8%)	0 (0%)	0.31
Surgical site infection	1 (1.9%)	0 (0%)	1
HD port	2 (3.8%)	0 (0%)	1
Urinary	1 (1.9%)	3 (13.0%)	1
Respiratory	1 (1.9%)	0 (0%)	0.08
Gastrointestinal	1 (1.9%)	1 (4.3%)	1
Unclear	14 (26.9%)	4 (17.4%)	0.52

Primary Outcome



15.4% (8/52) versus 17.4% (4/23)
p = 1

Secondary Outcomes

Outcome	MIC ≥ 2 mcg/mL (n=23)	MIC <2 (n=52)	P value
In-hospital, all cause mortality	13% (3/23)	11.5% (6/52)	p= 1
Duration of bacteremia (median)	1 days	1 days	p= 0.98 IQR: 1, 1
Hospital length of stay (median)	16 days	12 days	p= 0.69 IQR: 6, 27
Percentage of methicillin-resistant CoNS	78.3% (18/23)	50% (26/52)	p= 0.02

Patients With and Without ID Consult

Outcome	ID Consult* (n=51)	No ID Consult* (n=17)	P value
Scheduled duration of antibiotic therapy (median)	14	7	p= 0.03 IQR: 7, 17
Presumed metastatic infection	29.4% (15/51)	0% (0/17)	p= 0.01
Scheduled for 14-17 days of antibiotic therapy and treated as if uncomplicated *Staphylococcus aureus* bacteremia	66.7% (10/15)	66.7% (4/6)	p= 1

*Includes only patients with a set duration of therapy per documentation in EHR

Conclusions and Discussion

Conclusion

- A vancomycin MIC of ≥2 mcg/mL or <2 mcg/mL did not significantly affect clinical outcomes in patients with CoNS BSIs
- *S. epidermidis* was the most common CoNS species isolated
- *S. epidermidis* was the species most likely to have a vancomycin MIC of ≥2 mcg/mL
- Overall, 58.7% of CoNS isolates were methicillin-resistant

Study Limitations

- Small patient population included
- Single-center, retrospective study
- Lack of cases of CoNS infective endocarditis
- Did not stratify patient risk at start of therapy

Relevance to Practice

- Reinforces current practice in CoNS treatment based on IDSA MIC breakpoints
- Vancomycin remains an appropriate empiric antibiotic selection for CoNS with a vancomycin MIC of ≥2 mcg/mL or more
- Further research is needed to determine a true clinical relevance of higher vancomycin MICs in CoNS BSIs

What's next…

Future Direction

- Continue use of vancomycin as CoNS BSI empiric therapy
- Provide education to differentiate infection versus contamination when CoNS isolated
- Consider transition to alternative agent in CoNS IE if vancomycin MIC is ≥2 mcg/mL
- Continue assessment of appropriate therapy for CoNS BSI as new literature emerges
- Appropriately de-escalate antibiotics as appropriate based on susceptibilities

Acknowledgements

Research Team

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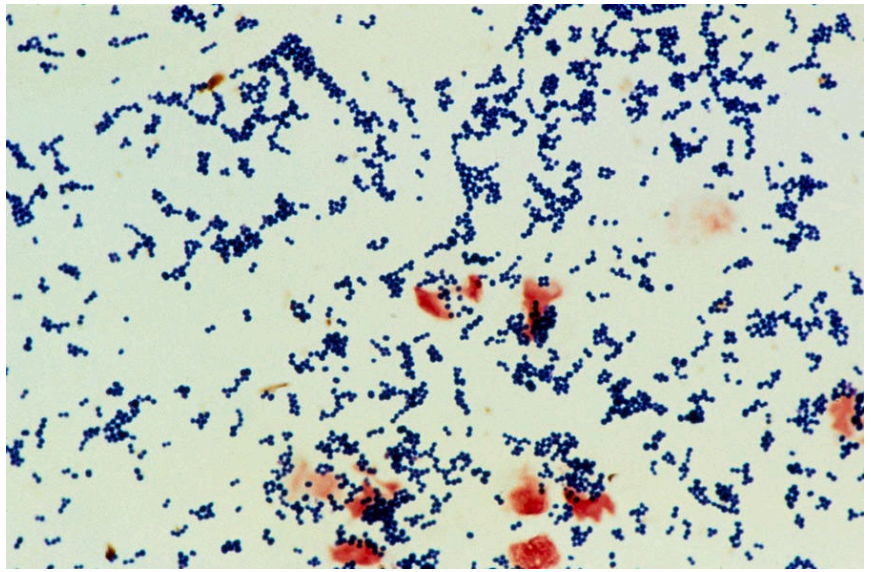

https://www.sciencephoto.com/media/12763/view

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June 2nd, 2023

Evaluation Reminder

Evaluation reminder for the 2023 Louisiana Office of Public Health Antimicrobial Stewardship Summit

Please use this QR code or log-on/type in the following URL: https://bit.ly/AMR2023

To use QR code:

- Open your phone Camera app from the Home screen, Control Center, or Lock screen.
- Select the rear-facing camera. Hold your device so that the QR code appears in the viewfinder in the Camera app.
- Tap the notification to open the link associated with the QR code.

Healthcare-associated Infections HAI Elimination Louisiana

LOUISIANA DEPARTMENT OF HEALTH