

Aminopenicillins versus Non-Aminopenicillins for Treatment of Enterococcal Lower Urinary Tract Infections

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HENRY FORD HEALTH

Introduction

- Ampicillin and amoxicillin are treatments of choice for *Enterococcus* sp., however *E. faecium* typically harbors aminopenicillin resistance
- The average urinary concentrations of amoxicillin are sufficient to overcome typical minimum inhibitory concentrations of 256 (interquartile range 8-256) mcg/ml and observational studies suggest aminopenicillins are promising for *E. faecium* lower urinary tract infection
- The purpose of this study was to compare aminopenicillins (AP) to non-aminopenicillins (NAP) for enterococcal lower urinary tract infections

Methods

Study Design and Endpoints

- IRB approved retrospective cohort study at Henry Ford Health comparing outcomes of definitive therapy with AP or NAP for *Enterococcus* sp. from 2013 to 2021.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> Inpatient adults ≥ 18 years old with symptomatic lower UTI Pyuria or leukocyte esterase on urinalysis Growth of <i>Enterococcus</i> sp. or <i>E. faecium</i> limited to urine, as documented above Treated with agent presumed to be active against <i>Enterococcus</i> sp. for definitive therapy (>50% of total duration; Antibiotics included: amoxicillin, ampicillin, amoxicillin/clavulanate, ampicillin/sulbactam, linezolid, daptomycin, nitrofurantoin, fosfomycin, doxycycline) 	<ul style="list-style-type: none"> Prior urine culture of any <i>Enterococcus</i> organism in previous year Review of systems unable to be completed to due mental status Asymptomatic bacteriuria (ASB) Urinary instrumentation (i.e., urostomy tubes), except for urinary catheter or stent Evidence of upper UTI, pyelonephritis, bacteremia, growth of enterococcus at another site or prostatitis Ongoing antibiotic prophylaxis, trauma to urinary system or newfound obstruction Renal transplant Definitive <i>E. faecalis</i> identification in urine culture

- Objectives:
 - Compare clinical and microbiological outcomes between AP and NAP therapies for enterococcal lower UTI through a non-inferiority design
 - Determine if AP therapy and/or other variables assessed were associated with clinical failure
- As part of a lean process antimicrobial stewardship strategy, Henry Ford Microbiology Lab does not routinely perform full susceptibility on *Enterococcus* sp. urine cultures:

>100000 CFU per ml *Enterococcus* sp.
Positive for Vancomycin resistant *Enterococcus* !
Ampicillin IV or Amoxicillin orally are predictably reliable for treatment of uncomplicated enterococcal UTI.

- Primary Endpoint:** 14- day clinical composite success at 14 days
 - Symptomatic Success: resolution of symptoms of UTI without new urinary symptoms
 - Microbiologic Success: no repeat culture demonstrating growth of the index species
- Analysis Plan: A non-inferiority analysis was performed. Multivariable logistic regression was conducted to identify independent factors associated with 14-day clinical composite failure
- A sample size of 178 patients was calculated assuming 85% success, one-sided alpha 0.025 and a non-inferiority margin of 15%

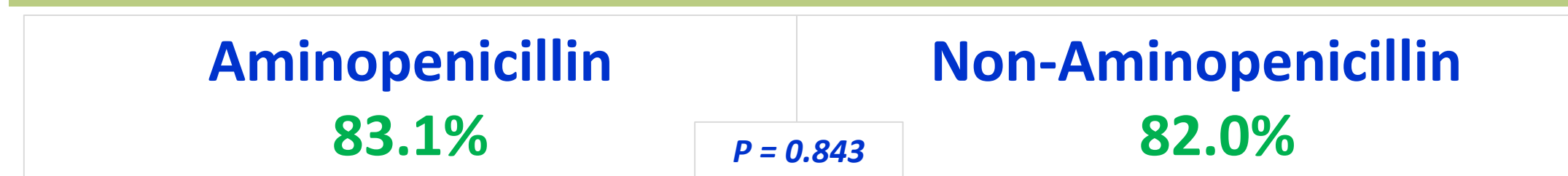
Results

Patient Characteristics

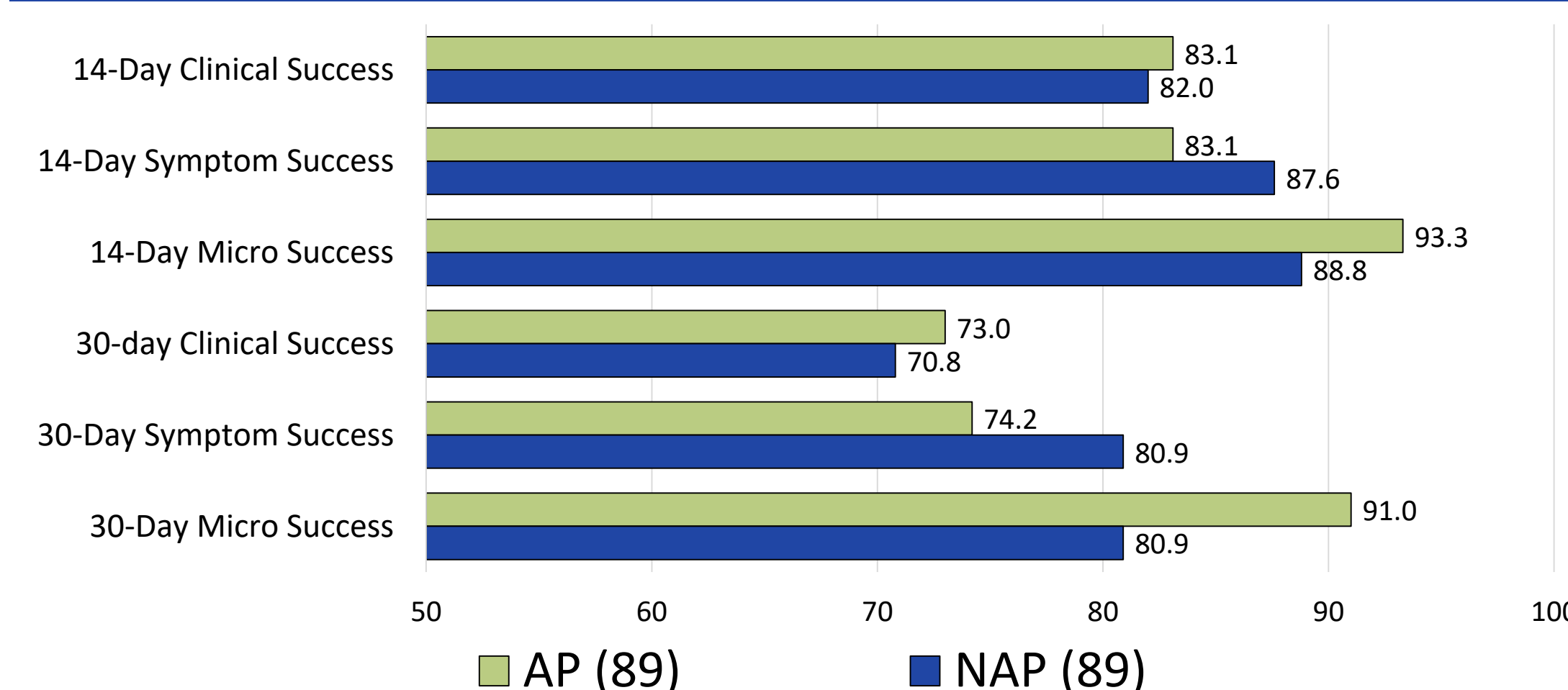
	All (178)	AP (89)	NAP (89)	P-Value
General				
Age	68 (58-78)	68 (57-77)	69 (60-78)	0.616
Sex, Female	119 (66.9)	61 (68.5)	58 (65.2)	0.633
Charlson Comorbidity Index	5 (4-7)	5 (4-7)	5 (4-7)	0.361
Comorbidities				
Diabetes	77 (43.3)	43 (48.3)	34 (38.2)	0.173
End Stage Renal Disease	10 (5.6)	4 (4.5)	6 (6.7)	0.747
Immunocompromised	26 (14.6)	16 (18.0)	10 (11.2)	0.203
Recent History UTI	41 (23.0)	20 (22.5)	21 (23.6)	0.859
Urinary Instrumentation				
Urolithiasis	21 (11.8)	11 (12.4)	10 (11.2)	0.816
Stent	25 (14.0)	13 (14.6)	12 (13.5)	0.829
Home Self-Cath	31 (17.4)	9 (10.1)	22 (24.7)	0.01
Infection and Treatment Characteristics				
Catheter Related	67 (37.6)	31 (34.8)	36 (40.4)	0.439
Community Onset	106 (59.6)	54 (60.7)	52 (58.4)	0.760
Days Definitive Antibiotics	3 (3-7)	5 (4-7)	5 (3-7)	0.682
Vancomycin Resistance	149 (83.7)	73 (82.0)	76 (85.4)	0.543
Definite ID of <i>E. faecium</i>	100 (56.2)	34 (38.2)	66 (74.2)	<0.001

Values expressed as n (%) or median (IQR)

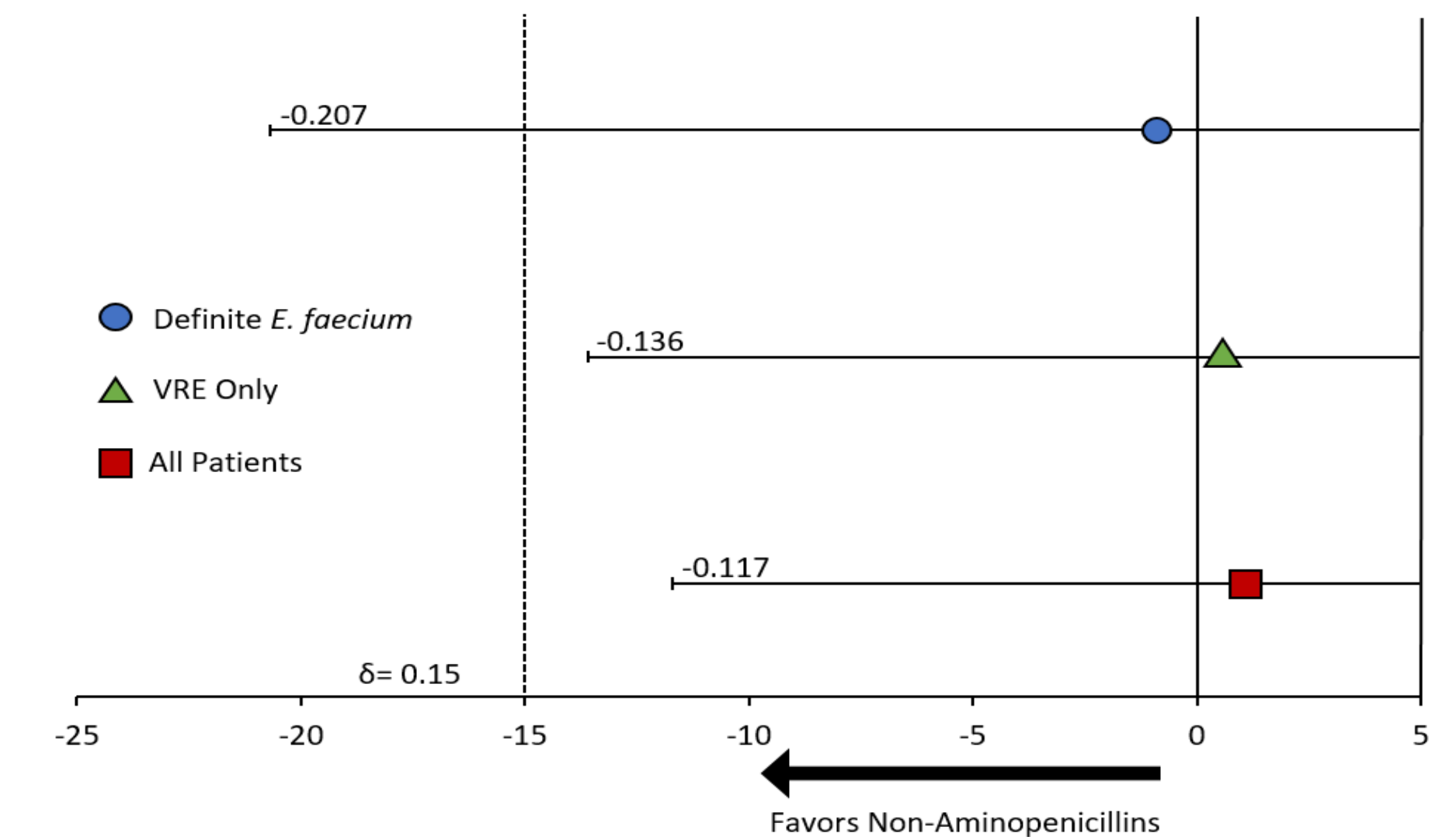
Percent Composite Clinical Success 14 Days



Percent Success at 14 and 30-Days Following Treatment for Enterococcal Lower UTI*



Forest Plot of All Patients and Subgroups for 14-Day Clinical Success Receiving Aminopenicillin and Non-Aminopenicillin Therapies for Lower Urinary Tract Infections Caused by *Enterococcus* sp.



Multivariable Logistic Regression for 14-Day Failure

	14-Day Failure (n=31)	OR (95% CI)	P-Value	aOR (95% CI)	P-Value
Aminopenicillin Therapy	15 (48.4)	0.93 (0.43 to 2.01)	0.843	0.84 (0.38 to 1.86)	0.663
Female Sex	24 (77.4)	1.88 (0.76 to 4.65)	0.169	1.77 (0.88 to 4.42)	0.222
Immunocompromised	8 (25.8)	0.40 (0.16 to 1.03)	0.052	0.40 (0.16 to 1.03)	0.058
End Stage Renal Disease	1 (3.2)	1.96 (0.24-16.03)	1.000	Not Tested	
Definitive <i>E. faecium</i>	20 (64.5)	1.52 (0.68-3.40)	0.303	Not Tested	
Vancomycin Resistance	27 (87.0)	1.38 (0.44-4.31)	0.574	Not Tested	
Diabetes	14 (45.2)	1.10 (0.50-2.39)	0.814	Not Tested	
Community Onset	19 (61.3)	0.92 (0.41-2.02)	0.838	Not Tested	
Catheter Related	11 (35.5)	0.89 (0.40-2.00)	0.785	Not Tested	
Procedure Related	9 (29.0)	1.30 (0.53-3.02)	0.564	Not Tested	

Summary

- Aminopenicillin therapy was not associated with 14-day failure in a multivariable logistic regression
- Aminopenicillins met non-inferiority criteria, supporting their role for lower UTIs due to enterococci
- More data specific to ampicillin resistant, confirmed *E faecium* lower UTI is needed