Is Empiric Coverage Necessary? Incidence of *Pseudomonas aeruginosa* and Methicillin-Resistant *Staphylococcus aureus* in Foot Infections

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Purpose

1. To determine the prevalence of *Pseudomonas aeruginosa* (PA) and Methicillin-resistant *Staphylococcus aureus* (MRSA) in wound cultures of foot infections at five hospitals in Southern California and compare to other geographic locations.
2. To examine several patient-specific variables and determine their ability to predict whether a foot infection is likely due to PA or MRSA.
3. To determine if empiric antibiotic coverage against PA or MRSA is warranted based on the current data and to utilize these data to bolster antimicrobial stewardship opportunities.

Introduction

Foot infections are a substantial burden on the healthcare system worldwide, especially diabetic foot infections. Most have been characterized as being polymicrobial with Staphylococcal and Streptococcal organisms the most frequent pathogens (1) although other organisms are frequently encountered. *Pseudomonas aeruginosa* (PA) and Methicillin-resistant *Staphylococcus aureus* (MRSA) have both been reported as common causes of foot infection with increasing frequency. With regard to PA, studies have cited the prevalence to be between 4-26%, with lower rates in the US (2-7). A recent meta-analysis of current literature found the prevalence of MRSA in diabetic foot infections to be 16.78% (8).

Despite formal recommendations to only provide empiric antibiotic treatment for PA and MRSA to those with established risk factors (9), we have observed a common trend of empirically covering for these organisms in the majority of foot infections in our region regardless of their risk profile. Patients with a foot infection, despite the level of severity, are often placed on a regimen of Vancomycin and Piperacillin/Tazobactam or Cefepime.

To our knowledge, the prevalence of PA and MRSA in foot infections has not been characterized in the literature with focus on the region of Southern California. If the incidence of PA or MRSA is low, this may be an opportunity to reduce empiric antibiotic coverage and help reduce the development of multi-drug resistant organisms (MDRO's) and costs within the healthcare system.

Methods

Study Design
Two-arm retrospective case-control study evaluating foot infections during 2018 at five hospitals in the Scripps healthcare system.
Patients were divided into a case group (patients with a foot infection and a culture positive for *Pseudomonas aeruginosa*) and a control group (patients with a foot infection that did not culture positive for *Pseudomonas aeruginosa*). The patients were divided into a second arm with a case group of patients with a foot infection with a culture positive for MRSA and a control group of those with a foot infection that did not culture positive for MRSA.
Data were extracted from medical records of all patients with a foot infection who were treated as inpatients in the Scripps Health system within 2018. Data was obtained from the first admission of the year which had adequate data if multiple admissions were documented; each patient was only evaluated one time for the current study.

Setting
Five hospitals within the Scripps Health system in San Diego, California.

Criteria
Inclusion criteria: 1) Foot infection treated as an inpatient at Scripps Health facilities during the year of 2018; 2) Have documented wound culture results.
Exclusion criteria: 1) Age <18 years.

Data Retrieval
Following Institutional Review Board approval, a list of ICD-10 codes which are commonly used for encounters relating to foot infections was compiled. The codes which were utilized in the search were: M86.(17,27,37,47,67,8X7), L97.(4,5) E11.621, E11.628 L08.9, L02.61, L03.0(3,4), M71.07, M65.07, M65.17, A48.0.

Variables
The following were collected for each patient: a) recent stay at a long-term care facility or hospitalization in last 90 days (y/n), b) Scripps location, c) whether surgery was performed (y/n), d) diabetes (y/n), e) ESRD (y/n), f) PAD (y/n), g) gender, h) age, i) body temp on admission, j) culture results, k) resistance profile, l) empiric antibiotic treatment, m) WBC n) ESR, o) CRP, p) Serum creatinine, q) blood culture results, r) surgical pathology results, s) duration of foot lesion, t) location of lesion, u) bone involvement (Probe to bone), v) IDSA classification.

Statistical Analysis
Descriptive statistics were performed to describe the study population's demographics and relevant medical history. Univariate analyses were used to identify factors associated with PA and MRSA in regards to the aforementioned variables. We used the t-test, chi-square test and Mann-Whitney U-test to determine significance of each of the variables. A multivariate analysis including all univariate factors with a p<0.10 was conducted using multivariate logistic regression for the outcome of PA and for MRSA. A statistically significant value was defined as a p-value of <0.05.

Results

The search returned 642 patient records based on the aforementioned ICD-10 data. Upon in-depth chart review, 310 of these met the inclusion criteria and were included in the final analysis.

Study results for the PA arm of the study are shown in tables 1-4. Study results for the MRSA arm of the study are shown in tables 5-8.

Discussion

Pseudomonas aeruginosa and MRSA are thought to be frequent pathogens in foot infections, however recent literature has estimated the incidence of both to be variable based on geographic location (2,9). Our study indicates that PA as a cause of foot infections is overall low (9.03%) in the Scripps system, which is reflective of the Southern California region. This is consistent with other data that have been published in the United States. Citron et al. found that the rate of PA in their study was 9.3% in the US while Young et al cited a PA rate of 4.5% (1,3). In contrast, Ertrugrul et al. in 2017 found that the rate of PA in foot infections in Turkey was 25.8% while Saseedharan et al found a rate of 20.9% in India (6). Some indicate that PA seems to be more common in African, Asian and Indian countries than in Europe or the United States (2). This will be an area for future research and we encourage further documentation of this kind in various geographic locations to provide a more complete understanding of this pathogen in foot infections. Our study indicates that MRSA as a cause of foot infections is moderate (17.74%) in the Scripps system. This is on par with a recent meta-analysis of foot infections published in 2019 (9).

Univariate analysis in our study indicated that patients with peripheral arterial disease and ulcerations located in locations other than the forefoot are significantly more likely to have a culture positive for PA. These failed to remain significant on multi-variate analysis. For MRSA, univariate analysis indicated that those with MRSA are significantly more likely to have a lower ESR, lower CRP and are less likely to probe to bone than non-MRSA patients. On multivariate analysis, bone involvement as defined by the probe to bone test remained significant.

Empiric anti-Pseudomonal and anti-MRSA antibiotic coverage is prevalent at Scripps Health, and the majority of this coverage was unnecessary. Given these findings, and the infrequency with which these organisms were found in blood culture, we recommend that providers forego empiric anti-pseudomonal and anti-MRSA coverage for foot infections in the majority of cases, unless there are specific risk factors for these organisms based on history and physical exam. These data will be utilized to inform antimicrobial stewardship opportunities in our healthcare system.

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Table 1

N=310		NO PSEUDOMONAS N=282		PSEUDOMONAS N=28		X-Squared	df	p
		n	%	n	%			
Long term facility/hospital stay last 90 days		78	27.66%	11	39.29%	1.6821	1	0.1946
Scripps Location						1.9733	4	0.7407
Surgery during this admission	201	71.28%	16	57.14%	2.4229	1	0.1196
Diabetic	223	79.08%	25	89.29%	1.6588	1	0.1978
ESRD	35	12.41%	5	17.86%	0.7409	1	0.3895
PAD	106	37.59%	16	57.14%	4.0807	1	0.0433
Gender	203	71.99%	17	60.71%	1.5706	1	0.2101
Temp on admission					2.8102	3	0.0936
Normal	264	95.31%	24	85.71%			
High	13	4.69%	4	14.29%			
Polymicrobial	223	79.08%	26	92.86%	3.0597	1	0.0802
Abx MRSA Coverage?	235	83.33%	27	96.43%	2.1306	1	0.1444
Abx Pseudomonal Coverage?	174	61.70%	25	89.29%	6.9494	1	0.0083
WBC					1.2184	3	0.7486
Low (<4)	5	1.78%	0	0.00%			
Normal (4-12)	177	62.99%	16	57.14%			
Elevated (12-18)	69	24.56%	9	32.14%			
Highly Elevated (>18)	30	10.68%	3	10.71%			
Blood Cultures					1.48E-29	1	
Positive	30	13.82%	3	13.04%			
Negative	187	86.18%	20	86.96%			
Surgical Path Results					0.055832	1	0.8132
Osteomyelitis	107	74.31%	8	66.67%			
No	37	25.69%	4	33.33%			
Medications					0.49344	1	0.4824
Insulin	128	65.64%	11	55.00%			
Other Meds	67	34.36%	9	45.00%			
Chronic foot lesion	14	4.96%	3	10.71%	0.70466	1	0.4012
Ulcer Location on foot (ankle/leg,heel, midfoot, forefoot, multi)					9.7317	4	0.0452
Ankle/Leg	17	6.12%	4	14.29%			
Heel	10	3.60%	3	10.71%			
Midfoot	26	9.35%	1	3.57%			
Forefoot	200	71.94%	15	53.57%			
Multi	25	8.99%	5	17.86%			
Probe to bone? (Y/N)					0.70466	1	0.4013
Y	93	56.36%	12	66.67%			
N	72	43.64%	6	33.33%			
IDSA Classification					6.2042	3	0.2868
None	8	2.86%	1	3.57%			
Mild	21	7.50%	2	7.14%			
Moderate	172	61.43%	17	60.71%			
Severe	72	25.71%	5	17.86%			
Insufficient Info	2	2.50%	3	10.71%			

	Mean (Median*)	SD (IQR*)	Mean (Median*)	SD (IQR*)	t (U*)	df	p-value
Age	61.19858	14.70068	65.36	14.21	-1.4318	308	0.1532
ESR within 1 week (MM/Hr)	63.56223	36.66668	77.31	28.53	-1.8488	257	0.0656
CRP within 48 hrs (Mg/L)	43.55*	121.28*	47.2*	137.85*	2478 *		0.4482
Creatinine within 24 hrs (Mg/dL)	1*	0.8*	0.9*	1.2*	3975 *		0.9032
A1c within 1 week (%)	8.25*	3.475*	6.85*	1.5*	2912.5 *		0.00254

Table 2 - Univariate Analysis

Pseudomonas

	Estimate	Std. Error	z value	Pr(>|z|)
Intercept	-2.48491	0.252439	-9.84359	7.31E-23
HOSP_STAY_90D	0.560099	0.409213	1.285623	0.198573
Intercept	-2.27592	0.240099	-9.44722	3.48E-21
LOC_1	-0.16117	0.426426	-0.37799	0.705471
Intercept	-2.34514	0.183277	-12.7929	1.87E-37
LOC_2	-0.05809	0.421175	-0.13793	0.890287
Intercept	-2.3979	0.217786	-11.0103	3.41E-28
LOC_3	0.640037	0.530955	1.205445	0.228032
Intercept	-2.27727	0.214337	-10.6247	2.29E-26
LOC_4	-0.20764	0.562826	-0.36892	0.712185
Intercept	-2.23978	0.235915	-10.2117	1.76E-24
LOC_5	-0.36403	0.513087	-0.70949	0.477973
Intercept	-1.90954	0.30932	-6.17335	6.69E-10
SURGERY	-0.62117	0.403923	-1.53785	0.124083
Intercept	-2.97893	0.591807	-5.03361	4.81E-07
DIABETIC	0.790629	0.628247	1.258454	0.208222
Intercept	-2.37389	0.218006	-10.8891	1.30E-27
ESRD	0.427984	0.525451	0.814509	0.415354
Intercept	-2.68558	0.298351	-9.00136	2.23E-19
PAD	0.784727	0.401183	1.955991	0.050474
Intercept	-1.97155	0.321819	-6.12628	9.00E-10
GENDER	-0.50844	0.409044	-1.243	0.213863
Intercept	-3.15634	0.905368	-3.90557	9.38E-05
AGE	0.013306	0.013597	1.42572	0.153946
Intercept	-3.97155	0.731875	-4.70714	2.51E-06
TEMP_NORM	-0.88352	0.578682	-1.52677	0.126787
Intercept	-2.35315	0.748261	-1.6509...	
POLYMICROBIAL	-1.235313	0.748261	1.65091...	
Intercept	-2.22462	0.526334	-4.22664	2.37E-05
NORMAL_WBC	-0.15241	0.401257	-0.38443	0.700633
Intercept	-1.79176	0.299572	-5.98106	2.22E-09
ESR	0.010613	0.005883	1.820203	0.068729
Intercept	-1.79176	0.239837	-7.82135	5.23E-15
CRP	0.001363	0.002283	0.597271	0.550404
Intercept	-2.44728	0.424918	-6.84797	4.98E-09
CREATININE	-0.06923	0.063556	-1.05929	0.289442
Intercept	-2.22462	0.382456	-5.81591	6.03E-09
SURG_PATH_OSTEO	0.060721	0.449626	0.135044	0.892576
Intercept	-1.79176	0.299572	-5.98106	2.22E-09
ULCER_FOREFOOT	-0.79851	0.401730	-1.98751	0.046864
Intercept	-2.48491	0.424918	-6.84797	4.98E-09
PROBE_TO_BONE	0.432441	0.514372	0.840679	0.400541
Intercept	-2.21161	0.219636	-10.0694	7.54E-24
IDSA_SEVERE	-0.45561	0.511984	-0.88999	0.373519

Table 3 - Multivariate Analysis

	Estimate	Std. Error	z value	OR	2.50%	97.50%	Pr(>|z|)
Intercept	1.112	1.1289	0.985	3.040475	0.366771	31.64572	0.32463
PAD	0.9333	0.4772	1.956	2.542908	1.008197	6.684073	0.05047
ULCER_FOREFOOT	-0.8576	0.4808	-1.784	0.424186	0.164563	1.105505	0.07448

Table 4

	Number	Percentage of Total
N=310 Pts		
Total PA Cultures	28	9.03%
Total PA in Monoculture	2	0.65%
Total Anti-PA Empiric ABX	199	64.19%
Appropriate Anti-PA Empiric ABX	25	8.06%
Undertreated for PA	3	0.97%
Overtreated for PA	174	56.13%

Table 5

N=310		NO MRSA N=255		MRSA N=55		X-Squared	df	p
		n	%	n	%			
Long term facility/hospital stay last		68	26.67%	21	38.18%	2.931	1	0.08689
Scripps Location						3.208	4	0.5236
Surgery during this admission	181	70.98%	36	65.45%	0.65784	1	0.4173
Diabetic	208	81.57%	40	72.73%	2.2103	1	0.1371
ESRD	36	14.12%	4	7.27%	1.3263	1	0.2495
PAD	100	39.22%	22	40.00%	0.01161	1	0.9142
Gender	179	70.20%	41	74.55%	0.41539	1	0.5192
Temp on admission (NA's = 5)					0.06990...	1	0.7915
Normal	238	94.07%	50	96.15%			
High	15	5.93%	2	3.85%			
Polymicrobial	207	81.18%	42	76.36%	0.66304	1	0.4155
Abx MRSA Coverage? (U's = 2)	218	85.49%	44	80.00%	0.78067	1	0.3769
Abx Pseudomonal Coverage? (U's =	170	66.67%	29	52.73%	3.5514	1	0.0595
WBC (NA's = 2)					3.4005	3	0.3339
Low (<4)	4	1.57%	1	1.85%			
Normal (4-12)	156	61.18%	37	68.52%			
Elevated (12-18)	64	25.10%	14	25.93%			
Highly Elevated (>18)	31	12.16%	2	3.70%			
Blood Cultures					8.79E-30	1	
Positive	28	13.86%	5	13.16%			
Negative	174	86.14%	33	86.84%			
Surgical Path Results					0.29504	1	0.587
Osteomyelitis	98	72.59%	17	80.95%			
No	37	27.41%	4	19.05%			
Medications					1.0313	1	0.3099
Insulin	119	66.11%	20	57.14%			
Other Meds	61	33.89%	15	42.86%			
Chronic foot lesion	14	5.49%	3	5.45%	8.05E-31	1	1
Ulcer Location on foot					6.6571	4	0.1877
Ankle/Leg	15	5.95%	6	11.11%			
Heel	9	3.57%	4	7.41%			
Midfoot	25	9.92%	2	3.70%			
Forefoot	180	71.43%	35	64.81%			
Multi	23	9.13%	7	12.96%			
Probe to bone?					7.3148	1	0.006839
Y	94	61.84%	11	35.48%			
N	58	38.16%	20	64.52%			
IDSA Classification					17.814	4	0.003189
None	5	1.96%	4	7.27%			
Mild	18	7.06%	5	9.09%			
Moderate	156	61.18%	33	60.00%			
Severe	69	27.06%	8	14.55%			
Insufficient Info	7	2.75%	5	9.09%			

	Mean (Median*)	SD (IQR*)	Mean (Median*)	SD (IQR*)	t (U*)	df	p-value
Age	61.59216	14.43988	61.49	15.9	0.046305	308	0.9631
ESR within 1 week (MM/Hr)	67.06422	36.28187	53.66	38.43	2.1961	257	0.02898
CRP within 48 hrs (Mg/L)	46.8*	152.1*	32.5*	36.5*	4874.5 *		0.02854
Creatinine within 24 hrs (Mg/dL)	1*	0.9*	0.55*	7137 *			0.7642
A1c within 1 week (%)	8*	3.5*	7.9*	2.3*	3100 *		0.3515

Table 6 - Univariate Analysis

MRSA

	Estimate	Std. Error	z value	Pr(>|z|)
Intercept	-1.70475	0.186439	-9.14375	6.03E-20
HOSP_STAY_90D	0.529179	0.311583	1.700228	0.089080
Intercept	-1.57455	0.185711	-8.4785	2.28E-17
LOC_1	0.115936	0.310027	0.373955	0.708438
Intercept	-1.61950	0.160954	-10.0619	8.14E-24
LOC_2	-0.05809	0.420175	-0.13829	0.890003
Intercept	-1.55814	0.158906	-9.80511	1.07E-22
LOC_3	0.208218	0.452894	0.459749	0.645696
Intercept	-1.41552	0.157505	-8.98710	2.50E-19
LOC_4	0.635159	0.496014	1.640447	1.00237...
Intercept	-1.60443	0.173278	-9.25908	2.05E-20
LOC_5	-1.35963	0.757187	-1.76111	0.078227
Intercept	-1.55364	0.315353	-0.80973	0.418094
SURGERY	-0.25535	0.315353	-0.80973	0.418094
Intercept	-1.10463	0.389245	-2.84668	0.004417
DIABETIC	-0.50656	0.343148	-1.47622	0.139860
Intercept	-1.45723	0.155408	-9.37757	6.75E-21
ESRD	-0.73990	0.545946	-1.36974	0.170809
Intercept	-1.66168	0.290838	-5.71341	1.11E-08
PAD	0.03279	0.309960	0.107982	0.914010
Intercept	-1.69168	0.290838	-4.65306	3.27E-06
GENDER	0.217862	0.334672	0.650942	0.515060
Intercept	-1.50493	0.541354	-2.34649	0.018953
AGE	-0.00047	0.008581	-0.05489	0.956228
Intercept	-1.22318	0.509747	-2.39947	0.016420
TEMP_NORM	-0.36427	0.533101	-0.68330	0.494450
Intercept	-1.39267	0.341253	-4.08107	4.48E-05
POLYMICROBIAL	-0.28880	0.355727	-0.81186	0.416827
Intercept	-1.70475	0.256225	-6.65306	2.87E-11
NORMAL_WBC	0.088128	0.345086	0.255389	0.798427
Intercept	-0.88603	0.275273	-3.21844	0.001287
ESR	-0.00593	0.002646	-2.24067	0.025047
Intercept	-1.48322	0.231212	-5.78387	7.31E-09
CRP	-0.00481	0.003926	-1.225	0.220593
Intercept	-1.30625	0.326146	-3.78347	0.000155
CREATININE	-0.01957	0.115601	-0.16927	0.865577
Intercept	-1.34821	0.259707	-5.16198	2.44E-07
SURG_PATH_OSTEO	0.524933	0.635300	0.82628	0.408623
Intercept	-1.33223	0.257916	-5.16336	2.40E-07
PROBE_TO_BONE	-1.06260	0.410827	-2.58643	0.009700
Intercept	-1.40471	0.198868	-7.06347	1.62E-12
IDSA_SEVERE	-0.77907	0.407591	-1.91159	0.055954

Table 7 - Multivariate Analysis

	Estimate	Std. Error	z value	OR	2.50%	97.50%	Pr(>|z|)
Intercept	-0.79158	0.48113	-1.645	0.453129	0.170601	1.142606	0.1
ESR	-0.00297	0.00802	-0.338	0.997032	0.979404	1.014152	0.7354
CRP	-0.00481	0.003926	-1.225	0.9952	0.986576	1.002273	0.2205
PROBE_TO_BONE	-1.01769	0.502561	-2.025	0.361428	0.129806	0.952342	0.0429

Table 8

	Number	Percentage of Total
N=310 Pts		
Total MRSA Cultures	55/310	17.74%
Total MRSA in Monoculture	13/55	23.64%
Total Anti-MRSA Empiric ABX	262/310	84.52%
Appropriate Anti-MRSA Empiric ABX	44/55	80%
Undertreated for MRSA	11/55	20%
Overtreated for MRSA	218/262	83.21%