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Original Contribution

Identification of risk factors for failure in patients with skin and soft tissue infections

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ABSTRACT

Purpose: The purpose was to determine significant predictors of treatment failure of skin and soft tissue infections (SSTI) in the inpatient and outpatient setting.
Methods: A retrospective chart review of patients treated between January 1, 2005 to July 1, 2016 with ICD-9 or ICD-10 code of cellulitis or abscess. The primary outcome was failure defined as an additional prescription or subsequent hospital admission within 30 days of treatment. Risk factors for failure were identified through multivariate logistic regression.
Results: A total of 541 patients were included. Seventeen percent failed treatment. In the outpatient group, 24% failed treatment compared to 9% for inpatients. Overweight/obesity (body mass index (BMI) > 25 kg/m^2) was identified in 80%, with 15% having a BMI >40 kg/m^2. BMI, heart failure, and outpatient treatment were determined to be significant predictors of failure. The unit odds ratio for failure with BMI was 1.04 (95% [Cl] = 1.01 to 1.1, $p = 0.0042$). Heart failure increased odds by 2.48 (95% [Cl] = 1.3 to 4.7, $p = 0.0056$). Outpatients were more likely to fail with an odds ratio of 3.36.
Conclusion: Patients with an elevated BMI and heart failure were found to have increased odds of failure with treatment for SSTIs. However, inpatients had considerably less risk of failure than outpatients. These risk factors are important to note when making the decision whether to admit a patient who presents with SSTI in the emergency department. Thoughtful strategies are needed with this at-risk population to prevent subsequent admission.
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1. Introduction

Hospital admissions for skin and soft tissue infections increased by 29% between 2000 and 2004 [1]. In 2004, skin and soft tissue infections accounted for approximately 870,000 hospital admissions in the United States [2]. One study revealed that skin and soft tissue infections incurred on average 3.81 additional hospital days and $14,794 excess hospitalization charges [3]. In the emergency department settings, skin and soft tissue infections are often treated with oral antibiotics, however studies have shown failure rates of oral antibiotics range from 10% to 24% [4-9].

Despite the alarming number of hospitalizations related to skin and soft tissue infections each year, appropriate antibiotic treatment and significant predictors of treatment failure are largely unknown [10]. Additional studies have shown fever, chronic leg ulcers or edema, and a prior history of cellulitis can lead to increased failure rates with both oral and intravenous antibiotics [7].

Due to an increased prevalence of skin and soft tissue infections leading to hospitalizations, identification of patients at risk of failing treatment is essential. As the incidence of skin and soft tissue infections rises in obese patients, so too does the need for additional antibiotic use [11,12]. With >1.9 billion adults worldwide considered overweight and over 600 million categorized as obese in 2014, treatment of this select population will need to be optimized [13,14].

The Centers for Medicare and Medicaid Services identify cellulitis as one of the six medical conditions linked to about 80% of potentially avoidable admissions. Not all admissions can be avoided. Patients at high risk for failure of outpatient treatment could be targeted. Early hospitalization for those who will inevitably fail, could lessen morbidity due to cellulitis. The resultant proposed decreased Medicare and Medicaid spending is in accordance with the primary goals of Centers for Medicare and Medicaid Services as they move forward with this initiative [15].

In this study, the primary objective was to assess risk factors for failure of antibiotic treatment within 30 days for skin and soft tissue infections of patients treated in a Veteran's Affairs Healthcare System. These risk factors are important aspects when considering admission for a patient with a skin and soft tissue infection.

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2. Patients and methods

2.1. Design

This was a single center, retrospective chart review of inpatients and outpatients treated for skin and soft tissue infections at the Veteran Affairs Western New York Healthcare System in Buffalo, NY (WNY VA Healthcare System). Patient's charts were identified through ICD-9 diagnostic codes [528.3, 681.10, 681.9, 682.0, 682.1, 682.2, 682.3, 682.5, 682.6, 682.7, 682.8, 682.9] or ICD-10 diagnostic codes [2.01, 2.11, 2.21, 2.31, 2.41, 2.51, 2.61, 2.81, 2.91, 3.01, 3.03, 3.11, 3.211, 3.31, 3.81, 3.90] for patients treated for cellulitis and abscess during the time period of January 1, 2005 to July 1, 2016. Each patient was included only on the first episode of skin and soft tissue infections if multiple treatments were observed.

2.2. Study population

Patients included in the study had a diagnosis of a skin and soft tissue infection as defined by ICD-9 or ICD-10 diagnostic codes. Patients included were 18–89 years of age and were prescribed an oral or intravenous antibiotic. All outpatients were dispensed an antibiotic from the VA pharmacy. Exclusion criteria consisted of those transferred from an outside hospital, if ICD code did not match the indication, and if the patient was treated for concurrent infections. Additional exclusion criteria consisted of skin infections (e.g. impetigo, carbuncles, folliculitis, furunculosis, psoriasis, mastitis, bursitis) and skin infections at location that required supplementary management (e.g. hand, genital, perirectal, catheter site, prosthetic site, surgical site, orbital). Patients with venous stasis disease and HIV/immunocompromised were also excluded.

2.3. Outcome measures

The primary outcome was failure of treatment for skin and soft tissue infections and associated risk factors for failure. Failure was defined as an additional prescription or admission to the hospital within 30 days of treatment for a skin and soft tissue infection in the same location as the original infection. Baseline demographics included age, gender, race, height, weight, body-mass index (BMI), temperature, creatinine clearance, long term care facility residence, methicillin-resistant *Staphylococcus aureus* nasal colonization, and comorbid conditions such as injection drug use, diabetes, heart failure, peripheral artery disease, hemodialysis, alcohol abuse, cirrhosis, prior vein harvest, and Charlson comorbidity index. Additional data collected included recent hospitalization within 30 days of original treatment for skin and soft tissue infection, antibiotic treatment including treatment duration, and type and location of infection.

Appropriate therapy was based on the probability that an antibiotic would cover the usual pathogen for each type of skin and soft tissue infection. It did not gage whether it was excessively broad. Appropriate treatment for an abscess was defined as an antibiotic which was susceptible to the culture of the drainage, if performed. If there was no culture, treatment was considered appropriate if it consisted of treatment for *S. aureus* including MRSA with vancomycin, clindamycin, doxycycline, trimethoprim/sulfamethoxazole, daptomycin or linezolid. If the patient had a groin or buttock abscess then amoxicillin/clavulanate acid was also considered appropriate. Treatment of cellulitis was considered appropriate if it consisted of a beta lactam, vancomycin, trimethoprim/sulfamethoxazole, daptomycin or linezolid.

2.4. Statistics

Bivariate analysis was used to compare baseline characteristics, comorbidities, severity of illness, and healthcare-associated risk factors of those patients who had treatment success compared to those who failed. Categorical data was analyzed using the chi-square test whereas continuous data was analyzed using the Student's *t*-test. Factors that differed significantly ($p < 0.05$) between the comparator timeframes were built into a multivariate logistic regression model, which was used to evaluate the impact of these variables on predicting risk factors for treatment failure. Statistical analysis was performed utilizing JMP software version 13. (Copyright 2015, SAS institute Inc., Cary, NC, USA.)

3. Results

A total of 4015 patient visits were reviewed using the Veterans Affairs Western New York (VA WNY) Healthcare System electronic medical record (EMR); 541 patients were included (Fig. 1). There were 248 patients (46%) treated as inpatient and 293 patients (54%) treated as outpatient. Cellulitis was treated in 385 patients (71%), abscesses were treated in 112 patients (21%), and mixed cellulitis and abscess were treated in 44 patients (8%). Of the combined population, 92 patients (17%) failed treatment with antibiotics for skin and soft tissue infections. In the outpatient treatment group, 69 patients (24%) failed as compared to 23 patients (9%) treated within the hospital ($p < 0.0001$).

The types of skin and soft tissue infection and locations were similar between the groups of patients who failed and succeeded. Lower extremity infections (66.5%) were the most prevalent in both groups. Incision and drainage (I&D) occurred in 50% of the cases of abscess/mixed infection. There was no difference in success or failure of treatment ($p = 0.68$). The incidence of I&D also did not differ between inpatients and outpatients. Sixty percent of inpatients had an I&D performed and 46% of outpatients had an I&D performed ($p = 0.1$).

Appropriate treatment was defined in broad empirical terms. The population consisted of 97% receiving an antibiotic which would cover the usual pathogens for cellulitis or abscess. The most common antibiotics in the outpatient setting included the following: trimethoprim/sulfamethoxazole ($n = 98$), cephalexin or cefpodoxime ($n = 89$), clindamycin ($n = 46$), clindamycin ($n = 46$), beta-lactam/beta-lactamase inhibitor ($n = 29$), dicloxacillin ($n = 10$), doxycycline ($n = 9$), cephalexin + trimethoprim/sulfamethozaxole ($n = 8$), azithromycin ($n = 2$), amoxicillin ($n = 1$), and PCN VK ($n = 1$). Inpatient antibiotics were most likely to be broad and include vancomycin + beta-lactam/beta-lactamase inhibitor ($n = 132$), vancomycin ($n = 58$), beta-lactam/beta-lactamase inhibitor ($n = 19$), vancomycin + cefazolin or ceftriaxone ($n = 14$), clindamycin ($n = 8$), cefazolin or ceftriaxone ($n = 7$), vancomycin + clindamycin ($n = 4$), cephalexin ($n = 1$), doxycycline ($n = 1$), daptomycin ($n = 1$), trimethoprim/sulfamethoxazole ($n = 1$), daptomycin and ertapenem ($n = 1$), nafcillin ($n = 1$). Overweight/obesity was common in the study population; 80% had a BMI >25 kg/m^2. One hundred forty-one patients (26%) were overweight (BMI of 25.0 to 29.9 kg/m^2) and 207 patients (38%) were obese (BMI of 30 kg/m^2 to 39.9 kg/m^2). Eighty-three patients (15%) had a BMI of 40 kg/m^2 or greater.

The subsets of patients who failed antibiotic therapy and those who succeeded were similar in terms of age, gender, race, and height (Table 1). The Charlson comorbidity index was similar between those who failed and those who succeeded; 89% had a Charlson score between 0 and 4. The incidence of diabetes was also comparable between both groups of patients. MRSA colonization was assayed in 306 patients in the total cohort. It was positive in 61 (20%) of those tested however it did not impact the success of treatment. Patients who failed were more likely to be obese, have a diagnosis of heart failure, a higher creatinine clearance, and to be treated as an outpatient. There were 92 failures, 75% were originally treated as an outpatient.

Significant risk factors for failure were included in the multivariate logistic regression analysis to determine each factor's effect on failure. Non-significant factors were eliminated in backwards fashion. Creatinine clearance ($p = 0.97$) was removed, as it was not statistically significant. Body mass index, heart failure, and outpatient treatment were

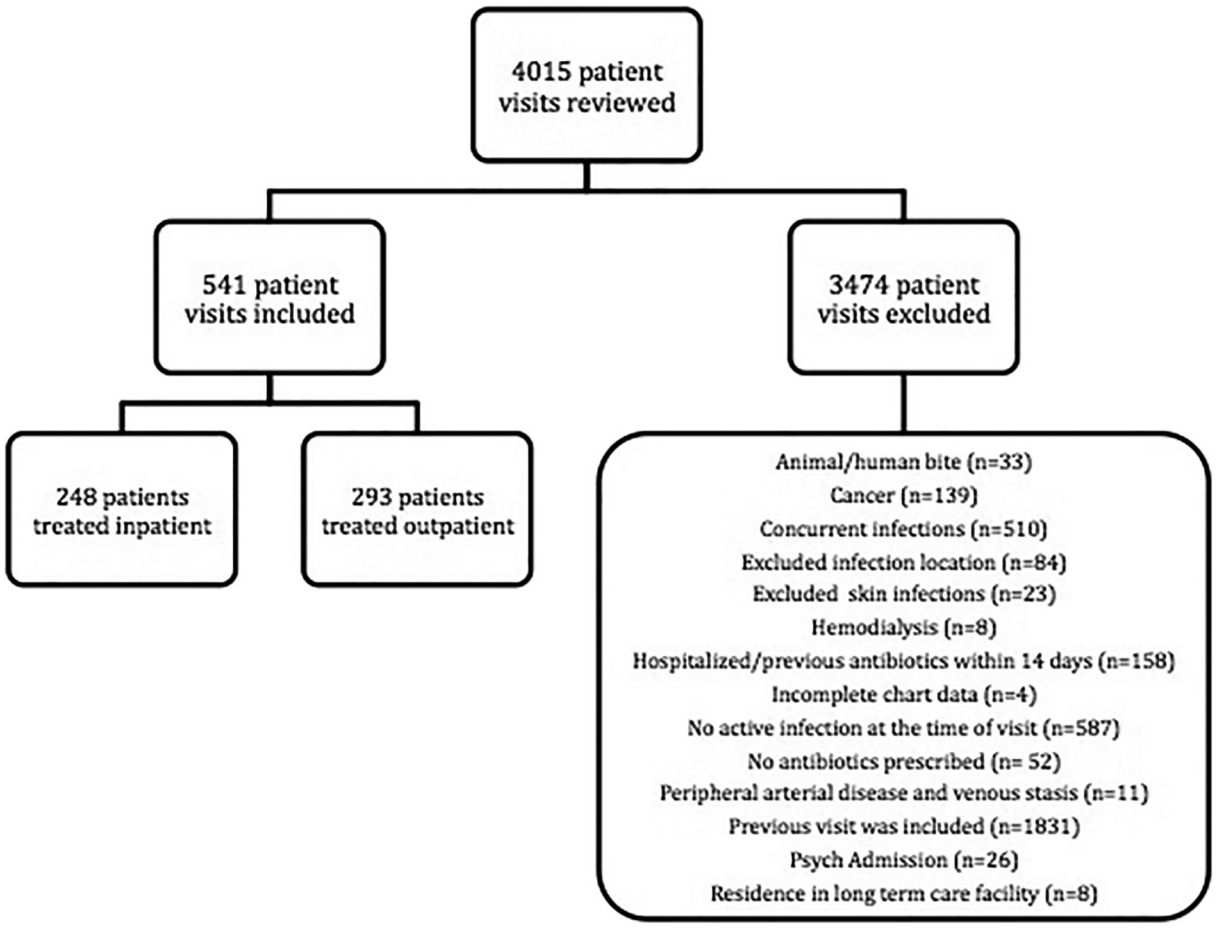

Fig. 1. Inclusion and exclusion.

significant predictors of failure. The unit odds ratio for failure with BMI was 1.04 (95% confidence interval [CI] = 1.01 to 1.1, $p = 0.0042$). Therefore, each 10-kg/m^2 unit increase in body mass index was associated with a 1.5-fold greater odds of failure. The odds ratio for heart failure was 2.48 (95% confidence interval [CI] = 1.3 to 4.7, $p = 0.0056$). Outpatients were more likely to fail when compared to inpatients with an odds ratio of 3.36 (95% confidence interval [CI] = 2.0 to 5.7, $p < 0.0001$). In patients with heart failure had a failure rate ranging from 11 to 38% whereas their counterparts without heart failure failed 5–20% of the time. Conversely, the outpatients in our cohort had a higher risk of failure. Those outpatients with heart failure experienced had failure 30–67% of the time. Those outpatients without heart failure failed 15–45% of the time (Table 2).

4. Discussion

Seventeen percent of the population failed treatment for skin and soft tissue infection. Our goal was to identify high-risk patients at risk for treatment failure. This information will be helpful in making the determination regarding admission for a patient who presents to the emergency department with skin and soft tissue infections. We found that not only are overweight/obese and heart failure patients at risk for failure of skin and soft tissue infections, but those treated as outpatients are more likely to fail.

Pharmacodynamics and pharmacokinetic characteristics of antibiotics are altered in obese patients, which may account for the increased risk of failure in these patients. Increased volume of distribution into adipose tissue, increased clearance, and insufficient antibiotic penetration may prevent oral antibiotics from reaching the desired site of action [16]. Patients with perfusion abnormalities due to increased BMI or heart failure are at an increased risk of failure and may not succeed with a standard course of oral antibiotics alone. Similarly, those with heart failure may have chronic edema in the lower extremities that predisposes them to cellulitis [17]. Reduced cardiac output and peripheral vasoconstriction leading to reduced volume of distribution and potentially poor penetration of antibiotic to infection site further hinders treatment success [17,18]. For these reasons, those patients with elevated BMI and those with heart failure represent patients who will benefit from more aggressive treatment. These patients may benefit from closer follow-up in the outpatient setting to ensure that they are improving to avoid subsequent admission. Alternatively, some of these patients may benefit from more expansive inpatient treatment.

Studies have shown patients with diabetes mellitus are at an increased risk for skin and soft tissue infections due to damage to lymphatic vessels and accompanying lower leg ulceration [10,19,20]. Interestingly, those with diabetes mellitus were not at an increased risk for failure in our study. Similar results were seen in a Miami Veteran's Affairs hospital that found lower extremity edema, body mass index, smoking, and homelessness as significant and independent risk factors associated with recurrent cellulitis [21]. Our study assayed the presence or absence of the diagnosis diabetes mellitus, rather than identifying patients based on HbA1c or glycemic control.

Outpatients were 3.36 times more likely to fail antibiotics for skin and soft tissue infections compared to their inpatient counterparts. This may seem counterintuitive, as sicker patients with skin and soft tissue infections should be more likely to be admitted. Hospitalization, however allows for intravenous antibiotics and potentially closer monitoring for targeted durations of therapy. Intravenous drug delivery is systemic avoiding absorption and bioavailability issues, highly potent [22]. High drug levels and rapid drug delivery with intravenous

Table 1
Baseline of patient characteristics and clinical data.

Factor	Total cohort $N = 541$	Failure $N = 92$ (17%)	Success $N = 449$ (83%)	p-Value
Age (years)	62.67 ± 16.25	60.67 ± 15.10	63.10 ± 16.46	0.20
Male	513 (94.82%)	91 (98.91%)	422 (93.99%)	0.05
Race				0.69
African American	77 (14.23%)	11 (11.96%)	66 (14.70%)	
Caucasian	455 (84.10%)	80 (86.96%)	375 (83.52%)	
Other	9 (1.66%)	1 (1.09%)	8 (1.78%)	
Height (in)	69.71 ± 3.39	69.61 ± 2.78	69.73 ± 3.51	0.77
Weight (kg)	99.74 ± 27.37	106.76 ± 29.96	98.30 ± 26.62	0.0076
Body Mass Index (kg/m^2)	32.05 ± 8.33	34.16 ± 8.88	31.62 ± 8.16	0.0085
Obese groups				0.0305
Normal	110 (20.33%)	15 (16.30%)	95 (21.16%)	
Overweight	141 (26.06%)	17 (18.48%)	124 (27.62%)	
Obese	207 (38.26%)	38 (41.30%)	169 (37.64%)	
Extreme obesity	83 (15.34%)	22 (23.91%)	61 (13.59%)	
Temperature (°F)	98.05 ± 1.46	97.81 ± 1.04	98.1 ± 1.53	0.09
Diabetic	223 (41.22%)	42 (45.65%)	181 (40.31%)	0.34
Heart failure	65 (12.01%)	17 (18.48%)	48 (10.69%)	0.036
Charlson score				0.39
0–4	484 (89.46%)	80 (86.96%)	404 (89.98%)	
5–10	57 (10.54%)	12 (13.04%)	45 (10.02%)	
Serum creatinine (mg/dL)	1.25 ± 0.93	1.15 ± 0.53	1.27 ± 0.99	0.27
Creatinine clearance (mL/min)	94.22 ± 50.89	106.60 ± 5.67	91.73 ± 49.31	0.0123
Provider location				0.0005
Emergency room	127 (23.48%)	30 (32.61%)	97 (21.60%)	
ICU	7 (1.29%)	1 (1.09%)	6 (1.34%)	
Medicine	232 (42.88%)	22 (23.91%)	210 (46.77%)	
Primary care	166 (30.68%)	39 (42.39%)	127 (28.29%)	
Surgery	9 (1.66%)	0	9 (2.0%)	
Duration of treatment (days)	10.77 ± 4.74	10.10 ± 2.26	10.92 ± 4.98	0.12
Location				0.79
Groin/buttock	34 (6.29%)	7 (7.61%)	27 (6.01%)	
Head/neck	64 (11.83%)	12 (13.04%)	52 (11.58%)	
Lower extremity	360 (66.54%)	63 (68.48%)	297 (66.15%)	
Multiple	3 (0.56%)	0	3 (0.67%)	
Trunk/abdomen	20 (3.7%)	2 (2.17%)	18 (4.01%)	
Upper extremity	60 (11.09%)	8 (8.70%)	52 (11.58%)	
Type of infection				0.52
Abscess	112 (20.70%)	20 (21.74%)	92 (20.49%)	
Cellulitis	385 (71.17%)	62 (67.39%)	323 (71.94%)	
Mixed	44 (8.13%)	10 (10.87%)	34 (7.57%)	
Adverse reaction to antibiotics	9 (1.66%)	3 (3.26%)	6 (1.34%)	0.19
Penicillin allergy	63 (11.65%)	12 (13.04%)	51 (11.36%)	0.65
Inpatient	248 (45.84%)	23 (25.0%)	225 (50.11%)	<0.0001
Outpatient	293 (54.16%)	69 (75.0%)	224 (49.89%)	
Hospitalized within 30 days	38 (7.02%)	25 (27.17%)	13 (2.90%)	<0.0001
Appropriate treatment	526 (97.4%)	89 (96.7%)	437 (97.5%)	0.66
MRSA Nares positive	61 (19.9%)	9 (22.5%)	52 (19.6%)	0.66
Antibiotic				0.07
Amoxicillin or PCN VK	2 (0.37%)	2 (2.2%)	1 (0.2%)	
Azithromycin	2 (0.37%)	0	2 (0.5%)	
Beta lactam/beta-lactamase inhibitor	48 (8.87%)	11 (12%)	37 (8.2%)	
Cefazolin/ceftriaxone	7 (1.29%)	0	7 (1.6%)	
Cephalexin/cefpodoxime	90 (16.6%)	19 (20.7%)	71 (15.8%)	
Clindamycin	54 (10%)	11 (12%)	43 (9.6%)	
Dicloxacillin	10 (1.9%)	1 (1.1%)	9 (2%)	
Doxycycline	10 (1.9%)	2 (2.2%)	8 (1.8%)	
Misc: daptomycin, ertapenem, nafcillin	3 (0.55%)	0	3 (0.7%)	
Trimethoprim/sulfamethoxazole	99 (18.3%)	26 (28.3%)	73 (16.3%)	
TMP/SMX + cephalexin	8 (1.5%)	1 (1.1%)	7 (1.6%)	
Vancomycin + Beta lactam/beta-lactamase inhibitor	132 (24.4%)	11 (12%)	121 (27%)	
Vancomycin + cefazolin/ceftriaxone	14 (2.6%)	1 (1.1%)	13 (2.9%)	
Vancomycin + clindamycin	4 (0.7%)	0	4 (0.9%)	
Vancomycin	58 (10.7%)	8 (8.7%)	50 (11.1%)	
I&D performed	78 (50%)	14 (46.7%)	64 (50.8%)	0.68

administration is favorable for patients with severe skin and soft tissue infections [23]. Patients under direct medical care ensure that medications are administered, possibly eliminating the risk of poor compliance in the outpatient setting. Furthermore, proper nursing care around the site of infection and elevation of lower extremities provides another added benefit to those hospitalized. Non-pharmacological treatment such as elevation of lower extremities promotes gravity drainage of edema and inflammatory substances that accelerates clinical improvement [24]. Therapy is individualized and streamlined in the hospital, whereas in the outpatient setting, it may be more empiric and inappropriate due to lack of monitoring and lack of microbiology data. Based on this study, closer follow-up is needed in patients with heart failure and who are obese to ensure success of therapy. Some of the same inpatient strategies can be suggested in the outpatient setting including leg

Table 2
Predicted failure rates with and without heart failure for inpatient and outpatients with various BMIs.

	Inpatient (intravenous antibiotics)		Outpatient (oral antibiotics)	
	No heart failure	Heart failure	No heart failure	Heart failure
BMI: 20 kg/m^2	4.8%	11.1%	14.5%	29.6%
BMI: 30 kg/m^2	7.0%	15.7%	20.1%	38.4%
BMI: 40 kg/m^2	10.0%	21.6%	27.2%	48.0%
BMI: 50 kg/m^2	14.1%	29.0%	35.6%	57.8%
BMI: 60 kg/m^2	19.6%	37.7%	45.0%	67.0%

elevation. The close follow-up in this targeted patient population may potentially avoid admission by targeting those at a higher likelihood for failure, for alternative therapies such as home intravenous antibiotics or potentially a long acting lipoglycopeptide.

Our study has several limitations. The retrospective study design relies on the accuracy of the electronic medical record and thus may be subject to selection bias. The use of ICD-9/10 codes to identify patients for inclusion relies on the strength of the clinician documentation and interpretation of the billing staff. The codes fail to capture the size and severity of infection which could influence the treatment outcome. The sizes of the lesions were not consistently documented, and it is probable that larger lesions will not be cured via antibiotics alone, though this study has insufficient information to prove this assumption. Though there is biologic probability for heart failure and obesity contributing to failure of treatment for skin and skin structure infections, it is possible that this group of patients had more exposure to the healthcare setting and thus was infected with more multi-drug resistant organisms. Infrequent culture data in our cohort made this hypothesis impossible to test. Patient adherence to medication and nonpharmacologic measures was unable to be assessed. The study was conducted in a predominantly older, male, Caucasian population. External validity may be limited, as this study was conducted at a single Veteran's Affairs institution.

5. Conclusions

This study identifies that patients with heart failure and obesity are at an elevated risk for failure and is an important consideration when making the decision whether to admit or discharged patients with skin and soft tissue infections who is seen in the emergency department. The failure rate of outpatients was higher when compared to inpatients. Initiatives to reduce unacceptably high treatment failure rates, especially in the outpatient setting are needed. Not every patient with cellulitis needs hospital admission, however patients who present to the emergency room with risk factors such as obesity with heart failure may require consideration for inpatient treatment of their skin and soft tissue infection. Specific route of medication administration, better treatment compliance, close monitoring, and enforcing nonpharmacologic treatment associated with inpatient stays is essential to preventing failure in the outpatient setting. Optimizing how and where these patients are treated can ultimately prevent failure in this susceptible population.

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Conflict of interest

The authors report no conflicts of interest.

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