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Finding the Niche: An Interprofessional Approach to Defining Oritavancin Use Criteria in the Emergency Department

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Keywords

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1. Introduction

Acute bacterial skin and skin structure infections (ABSSSI), such as cellulitis, are commonly evaluated in the Emergency Department (ED), accounting for approximately 3% of all visits.[1] Additionally, hospitalizations due to ABSSSI have doubled in incidence between 1998 and 2013. The cost has increased by 118% during this time.[2] Taken together, these data demonstrate the significant burden of ABSSSI on health care in the United States.

Oritavancin is a long-acting lipoglycopeptide antibiotic which received FDA-approval in 2015 for the treatment of ABSSSI in adult patients based on studies demonstrating noninferiority to intravenous (IV) vancomycin.[3,4] Administered intravenously over 3 hours, this agent provides an entire treatment course (up to 10 days) for ABSSSI with one dose and demonstrates excellent *in vitro* activity against the most common causative gram-positive pathogens (methicillin resistant *Staphylococcus aureus*, methicillin susceptible *Staphylococcus aureus*, group A *Streptococcus*). Previous statistical models describe potential cost savings with outpatient oritavancin treatment compared to inpatient treatment with IV antibiotics.[5]

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Oritavancin use in the ED may reduce unnecessary hospital admissions as over 40% of participants in the original trials were managed in the outpatient setting with a treatment failure rate similar to that of IV vancomycin.[6] Patient satisfaction surveys have also shown that patients with ABSSSI prefer to receive treatment in the outpatient setting.[7] However, since being approved, there is a paucity of implementation focused research aimed at identification of patients that would be optimally suited to receive this antibiotic. As there are no validated criteria to guide the need for hospital admission in non-septic patients with ABSSSI, it is unclear exactly which patients could safely be managed as outpatient after receiving oritavancin. This is further complicated by ED throughput concerns (3-hour infusion time) and a need to balance the socio-economic implications of hospital admission versus the cost of oritavancin. Thus, there is a critical need for the development of criteria to define and identify patients appropriate to discharge after receiving oritavancin in the ED and thus prevent a potentially avoidable admission (PAA).

The purpose of this study was to define the population of ED patients with cellulitis who would be most appropriate to receive oritavancin. This was achieved by a multidisciplinary consensus process to first define appropriate cellulitis admission criteria followed by a detailed analysis of patients admitted through the ED with cellulitis for presence of these criteria. These results were utilized to generate an oritavancin patient selection algorithm which incorporates relevant patient level inclusion and exclusion criteria (Figure 1).

2. Methods

This was a descriptive, retrospective study conducted at a Midwest healthcare system with two EDs (tertiary care, level 1 trauma academic medical center and a community ED). The study met the Institutional Review Board criteria for exempt research. All adult patients (aged 18 years and older) admitted from the ED to an inpatient ward with a primary admission diagnosis of cellulitis from January 1st to December 31st, 2016 were included. We did not include patients discharged from the ED or admitted to the ED observation unit in this analysis. Patients were identified via the electronic health record (Epic, Verona WI) using ICD-10 code L03 (cellulitis and acute lymphangitis).

A list of risk factors for outpatient ABSSSI treatment failure, absolute ABSSSI admission criteria, and oritavancin exclusions were defined *a priori* based on a multidisciplinary consensus process involving experts in pharmacy, infectious diseases, and emergency medicine. This involved a comprehensive review of available literature regarding oritavancin and drivers of ED disposition decision-making for ABSSSI, including risk factors for outpatient treatment failure (Table 1).[8–12] The group consensus on oritavancin exclusion criteria was any type of ABSSSI without a specific approved indication or patient allergy to lipopeptide antibiotics (Table 2). The group consensus was then to distinguish between absolute indications for admission (sepsis, septic shock, and admission for reason other than the ABSSSI) and risk factors for outpatient treatment failure which drive disposition decision making (Table 2). Sepsis was defined as concern for infection plus a systemic inflammatory response syndrome (SIRS) score ≥ 2 . Shock was defined as sepsis in addition to a medication order in the ED for a vasoactive continuous infusion.[13] Examples of non-cellulitis reasons for admission included uncontrolled pain, hyperglycemia, and need for

surgical debridement (e.g. concern for necrotizing infection). Patients who did not meet these established absolute admission indication criteria were deemed a PAA.

Detailed chart review was conducted by a clinical pharmacist using a standardized data collection instrument. The abstracted data included baseline demographics, Charlson comorbidity index (a commonly utilized comorbidity summary measure), [14] length of stay, antibiotic therapy, risk factors for outpatient treatment failure (Table 1), and reason for admission. Immunosuppression was considered a risk factor for treatment failure and defined as receiving active immunosuppressive medications (prednisone equivalent >20 mg/day, tacrolimus, cyclosporine, mycophenolate mofetil) or bone marrow transplant within the previous 6 months. If the primary reason for admission was not cellulitis, these cases were not classified as a PAA. A second reviewer, an attending emergency medicine physician, independently reviewed any patient that did not objectively meet valid admission criteria to definitively determine a PAA. There were no instances of disagreement in PAA assessments between the two reviewers. These variables were analyzed on a population basis via descriptive statistics including measures of frequency and central tendency. Between groups, continuous variables were analyzed using paired T-test, and categorical variables were analyzed using chi squared test. All calculations were completed using GraphPad statistical software. Missing data were considered null for descriptive characteristics and for lab values; missing data were omitted in calculating averages.

3. Results

Eighty-six patients were identified during the study period. Nine patients (10.5%) were deemed a PAA. The most prevalent admission criteria was sepsis or septic shock (45%), followed by admission for a reason other than cellulitis (38%), and infection type not suitable for oritavancin treatment (17%). The most common risk factors for outpatient treatment failure amongst the entire study population were antibiotics in past 90 days (47%), chronic leg ulcers/lymphedema (42%), diabetes (41%), and increasing infection severity despite antibiotics (34%). Medication nonadherence concern was documented for 16 patients (17%). Sixty-three patients (73%) had a Charlson comorbidity index ≥ 2 , meaning the estimated 10-year survival was $\leq 90\%$.

PAAs were further characterized and compared to the non-avoidable admission population (Table 3). A majority of the PAA population had cellulitis of an extremity (88%), diabetes mellitus (55%), and antibiotic use within the last 90 days (55%). This group was significantly younger than the non-PAA group (42.2 vs 58.6 years; $P=0.01$). There were no differences between the PAA group and the non-PAA group in regard to non-age demographics, number of risk factors for outpatient treatment failure (2.3 vs 1.9; $P=0.42$), Charlson comorbidity index ≥ 2 (55% vs 75%; $P=0.24$), average length of stay (80.8 vs 68.6 hours; $P=0.49$), antibiotic use in last 90 days (55% vs 45%; $P=0.73$), or diabetes (55% vs 39%; $P=0.48$).

4. Discussion

Oritavancin is a newly available parenteral antibiotic with the potential for use in the ED to avoid hospital admissions given its extended spectrum against the most common cellulitis pathogens and its approval for one dose curative therapy. After accounting for patients who are systemically ill due to the infection (sepsis) or have alternate reason for requiring hospital admission, emergency care providers make a disposition decision (inpatient versus outpatient management) based on perceived risk of treatment failure.[8,15] An often utilized ED quality metric is “bounce-backs” or patients who return 48 to 72 hours after an initial ED visit for the same complaint.[16,17] With this in mind, cellulitis patients perceived as high risk are typically admitted to the hospital for parenteral therapy despite studies which suggest this may not improve outcomes and the very low baseline mortality observed with these infections in both observation and interventional clinical trials (<1%).[3,4,10,18–22]

Until the approval of oritavancin and similar agents (dalbavancin, telavancin), the only alternative to hospitalization would be outpatient parenteral antimicrobial therapy (OPAT) which, although safe and effective, is logistically problematic in the ED environment and not widely implemented from this setting.[23–25] While our institution offers OPAT, this is limited to patients in the inpatient setting, as coordinating insurance, social work and patient evaluation is a significant barrier to efficient use in the ED setting. While other institutions have described successful ED to OPAT referral programs, the availability of long acting antibiotics such as oritavancin has truly opened up a new treatment pathway that requires further investigation.[26] The focus of these efforts should in part focus on the development of patient selection criteria that can be incorporated into pathways for EDs looking to implement this novel therapy. We studied patients at a single academic health system to identify potentially avoidable cellulitis admissions and found that at least 10.5% of patients met criteria for oritavancin use and our *a priori* definition of a PAAs. This is notably lower than a study by Talan et al, which, using a physician survey, identified “need for IV antibiotics” as the only reason for admission in 41.5% of ABSSSI. While our PAA rate is substantially lower and thus more conservative, the difference is likely accounted for by our use of SIRS criteria to define sepsis and a substantially higher rate of patients in our sample whose primary reason for admission was not their ABSSSI.

As a group, PAA patients were significantly younger and had higher rates of extremity cellulitis, diabetes mellitus, and recent antibiotic utilization. This finding is consistent with our selection of a lower risk population by establishing two absolute indications for admission that reflect severity of illness and medical complexity (sepsis criteria and need for admission unrelated to the ABSSSI). Ultimately, is it those patients with no absolute justification for admission (i.e., perceived risk of treatment failure drives the admission) who are most likely to benefit from admission avoidance via oritavancin administration.

There are many antibiotic options for treatment of cellulitis, including oral options for uncomplicated cases. Unfortunately, some of these patients are at risk for non-compliance or therapy failure. Our study identified patients with risk factors for outpatient oral antibiotic treatment failure but no other valid admission criteria as the ideal candidate for oritavancin

administration. Using our institution-specific data, we developed an ED oritavancin flowchart to facilitate identification and use of oritavancin in this setting (Figure 1).

Potential cost-savings to the health system have been described with the use of oritavancin to prevent these associated admissions and ED bounce backs, adding additional benefit to accurately identify these patients. A cost-minimization study estimates that the use of oritavancin in the outpatient setting may save up to \$6,475 per patient, as compared to inpatient treatment with vancomycin.[5] This associated cost savings is dependent on the patient's Charlson comorbidity index and symptoms on presentation, making it increasingly important to define the patient population in which oritavancin use is most appropriate. Telavancin, an alternative lipoglycopeptide, is a daily infusion and is not feasible for simplifying outpatient therapy. Dalbavancin, offers a single dose alternative for the treatment of ABSSI, although at the time of this study only a two-dose series was approved for this indication.[27] Finally, survey research indicates that ED patients prefer single dose intravenous antibiotic therapy followed by discharge when presented with various treatment options for ABSSI. Thus, if used with appropriate case selection guidance, oritavancin may also represent an safe and economic means of increasing patient centered care for a subset of ED patients with ABSSIs.[27]

Our study is not without limitations. First, it is retrospective in nature with a relatively small sample size from a single system, limiting generalizability. Second, data was collected via the use of a single data abstractor, potentially resulting in inherent biases present in the abstractor's methods. Third, there were instances in which information on patient comorbidities or laboratory data were not present. This may have biased the results as laboratory test averages did not include patients in whom these tests were not performed and in the absence of confirmatory information comorbidities were considered to be absent. Despite these limitations, this study provides a useful framework to start defining a niche for oritavancin use in the ED that balances emergency care provider concerns with outpatient treatment failure, antimicrobial stewardship and cost saving considerations. Similar assessments should be performed on larger patient samples with a specific lens of optimizing oritavancin patient selection criteria.

5. Conclusion

This retrospective study of 86 patients admitted to an inpatient unit through our ED with ABSSI found that 10.5% of admissions are PAAs. Oritavancin may be a reasonable treatment option for this patient population if one or more risk factors for outpatient treatment failure are present in the absence of any absolute indication for inpatient admission. While this study helps to define an appropriate patient population for the use of oritavancin, prospective studies are needed to examine the safety of these selection criteria in the ED as a strategy to avoid low value hospital admissions.

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Figure 1:
Algorithm for Identification of Patients Suitable for Oritavancin Therapy in the Emergency Department

Table 1:**Risk Factors for Outpatient Treatment Failure**

1.	Adherence concerns
2.	Acquired immunodeficiency syndrome
3.	Injection drug user
4.	Cognitively impaired
5.	Chronic edema
6.	Chronic leg ulcers
7.	Cirrhosis
8.	Duration of infection > 7 days
9.	Skin infection at same site within last 3 months
10.	Infection worsening despite antibiotic therapy
11.	Incarcerated
12.	Diabetes mellitus
13.	Immunosuppression

Table 2:**Oritavancin Exclusion Criteria**

1. Infection not suitable for treatment with oritavancin
• Bite wounds
• Orbital cellulitis
• Necrotizing fasciitis
• Suspected osteomyelitis
• Burn-related infections
• Diabetic foot infection
• Suspected polymicrobial infection
2. Severe allergy to antibiotic in lipopeptide family
• Oritavancin
• Vancomycin
• Daptomycin
• Telavancin

Table 3:

Subject Characteristics

	All Patients Admitted (N=86)	Non-Avoidable Admissions (N=77)	Potentially Avoidable Admissions (N=9)	P-value
Male, n (%)	51 (59)	44 (57)	7 (78)	0.29
Age (mean, years)	56.9	58.6	42.2	0.01
Race, n (%)	77 (90)	70 (91)	7 (78)	0.24
Caucasian	8 (9)	6 (8)	2 (22)	0.20
African American	1 (1)	1 (1)	0 (0)	1
Asian				
Diabetes mellitus, n (%)	35 (41)	30 (39)	5 (55)	0.48
Immunosuppressive medications, n (%)	19 (22)	17 (22)	2 (22)	1
Length of hospital stay (mean, hours)	79.5	80.8	68.6	0.49
Charlson Comorbidity Index 2, n (%)	63 (73)	58 (75)	5 (55)	0.24
Antibiotic use in past 90 days, n (%)	40 (47)	35 (45)	5 (55)	0.73
Chronic leg ulcers or edema, n (%)	36 (42)	32 (42)	4 (44)	1
Abscess, n (%)	23 (27)	20 (26)	3 (33)	0.69
Surgery consult, n (%)	35 (41)	32 (42)	3 (33)	0.73
Medication nonadherence concern, n (%)	16 (17)	15 (19)	1 (11)	1
Increasing infection severity despite antibiotics, n (%)	(34)	24 (31)	5 (55)	0.14
Valid admission criteria, n (%)	35 (41)	35 (45)	-	-
Sepsis or septic shock	29 (34)	29 (38)	-	-
Admission for other significant comorbidities	13 (15)	13 (17)	-	-
Infection not suitable for oritavancin treatment				