



ORIGINAL RESEARCH

Dalbavancin Reduces Hospital Stay and Improves Productivity for Patients with Acute Bacterial Skin and Skin Structure Infections: The ENHANCE Trial

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ABSTRACT

Introduction: Admissions for acute bacterial skin and skin structure infections (ABSSSI) are often prolonged because of intravenous (IV) antibiotics. Use of a long-acting IV antibiotic may reduce length of stay (LOS) on a hospitalist service. The ENHANCE ABSSSI trial sought to determine the impact on LOS and work productivity in patients treated with a long-acting IV antibiotic, dalbavancin, vs. usual care at an urban tertiary-care center.

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Methods: A single-center, pre- vs. post-period pragmatic trial at Weill-Cornell Medical Center assessed usual care for consecutively enrolled admitted ABSSSI patients during an observational period (pre-period). Identification and treatment of eligible admitted ABSSSI patients with dalbavancin were implemented in the post-period. Those with life-threatening infections, requiring multiple antibiotics/intensive care, or with unstable comorbidities were excluded. Outcomes were assessed over a 44-day follow-up period.

Results: Of 48 and 43 patients enrolled, respectively, in the pre- and post-periods, mean infection-related LOS was reduced in the post-period (3.2 days vs. 4.8 days; $P = 0.003$). Similar results were found in an adjusted LOS analysis. Work productivity and activity impairment outcomes significantly improved in the post-period ($P \leq 0.01$). Complete response rates were

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similar: 50% (pre-period) and 57% (post-period). Among AEs identified, 17% ($n = 7$) were found to have possible causal relation to dalbavancin in the post-period. Few AEs were serious ($n = 3$; 7% post-period versus $n = 1$; 2% pre-period).

Conclusion: After implementing the ENHANCE ABSSSI pathway, LOS was significantly reduced by almost 2 days, with potential improvements in work productivity and ability to complete daily activities.

Trial Registration: ClinicalTrials.gov identifier, NCT03233438.

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Keywords: Acute bacterial skin and skin structure infection; Cost; Dalbavancin; Long-acting antibiotic

Key Summary Points

Why carry out this study?

Admissions for acute bacterial skin and skin structure infections (ABSSSI) are often prolonged because of administration of intravenous (IV) antibiotics

Use of a long-acting IV antibiotic, dalbavancin, may reduce length of stay (LOS) on a hospitalist service when compared to usual care

What was learned from the study?

Determined the impact on LOS and work productivity in ABSSSI patients treated with long-acting IV antibiotic therapy vs. usual care at an urban tertiary-care center

After implementing the ENHANCE ABSSSI pathway, LOS was significantly reduced by almost 2 days and improved patient's work productivity and the ability to complete daily activities

Implementation of the ENHANCE ABSSSI pathway could have a significant impact on hospital cost and efficiency

INTRODUCTION

Quality of care and efficiency are paramount to improving US healthcare systems, particularly in the high-cost inpatient setting where hospitalists practice. Hospital admissions are under evaluation through a number of measures and must be critically assessed for improvement [1]. Care for acute bacterial skin and skin structure infections (ABSSSIs) has traditionally involved routine hospital admission and potentially prolonged hospital length of stay (LOS). The primary reason for hospitalization is the need to receive intravenous (IV) antibiotic therapy [2], despite the majority of ABSSSIs being non-life-threatening compared with other infections [3, 4]. ABSSSIs comprise as much as 2% of all US hospital admissions, causing a substantial burden to US hospitals, largely due to room and board costs [5]. ABSSSIs also commonly occur among employed adults (18–44 years of age) [5–7]; patients would value the option to complete ABSSSI treatment at home to avoid interference with daily activities and work [8].

Current guidelines support shifting ABSSSI care to outpatient settings for appropriate patients to improve hospital efficiency and reduce cost [4, 9–12]. However, operational barriers exist to shifting care to outpatient settings for many hospitals in the emergency department (ED). Implementation may suffer from lack of feasibility in care coordination between ED physicians and Antimicrobial Stewardship Teams before admission or because of high patient flow through many EDs.

For certain hospitals, ABSSSI treatment with a long-acting antibiotic once patients are admitted to the hospital floor and are stabilized is a potential option to facilitate discharge. Among those admitted for ABSSSI, those who may be eligible for early discharge would have few risk factors for readmission or ED care [4, 9, 11–13]. Careful patient selection is necessary to support efficiency and to ensure that treatment outcomes are similar versus standard care.

We reasoned that a long-acting lipoglycopeptide may be utilized to facilitate discharge for eligible patients because of an abbreviated

administration schedule [9, 12, 14], allowing patients to finish their treatment course in the outpatient setting [4, 10]. Long-acting antibiotics, such as dalbavancin, are administered either as a single 30-min parenteral infusion or two 30-min infusions once a week for 2 weeks [15, 16] or, in the case of oritavancin, as a 3-h infusion [17]. Long-acting antibiotics may improve patient and health system convenience as well as reduce risks of infection from the peripheral or central catheter lines that are used for some patients to receive daily parenteral antibiotics. Additionally, single-dose antibiotic treatment of ABSSSI is aligned with patient preferences [8], which are increasingly important as patient satisfaction is included in CMS hospital quality measures [18].

ENHANCE (A Pragmatic Trial Designed to Evaluate a New Critical Pathway for Treatment of Patients with ABSSSI) was a controlled trial that sought to determine the impact on LOS and work productivity in patients treated with the long-acting IV antibiotic, dalbavancin, vs. usual care at an urban, tertiary care center.

METHODS

Study Design and Setting

ENHANCE was a single-center, pre- versus post-period pragmatic trial (NCT03233438) conducted at New York-Presbyterian/Weill Cornell Medicine (NYP/WCM), a university-based urban medical center with > 1000 hospital beds, almost 50,000 hospital admissions, and nearly 75,000 ED visits per year. At the start of the trial, the site did not have dalbavancin routinely available.

The ENHANCE study design consisted of an initial observational period (pre-period); second, an interventional period (post-period) was subsequently implemented. In the pre-period only, treating physicians were not included in the study enrollment decision or trained on the protocol to prevent biasing the provision of usual care, which was defined as site or physician's usual care for ABSSSI. Once the pre-period was completed, site-training materials were provided to the study team on the post-period

of the study. Post-period training materials were based on the study protocol and prior literature [19]. Over a 2–4 week period, principal site investigators (MM and TW) trained treating physicians and staff; training was documented before beginning the post-period of the study. During the post-period, a separate set of enrolled patients was treated, which included (1) ABSSSI patient identification (inclusion/exclusion criteria applied) and (2) long-acting antibiotic treatment, administered as a single intravenous (IV) dose of 1500 mg dalbavancin over 30 min; patients with renal impairment (creatinine clearance < 30 ml/min) and no regularly scheduled dialysis received a single IV dose of 1125 mg dalbavancin over 30 min [15]. All patients enrolled in the post-period received dalbavancin. At the discretion of the treating physicians, patients were discharged from the hospital to an outpatient setting after receipt of dalbavancin. While randomization at the site level at NYP/WCM was not feasible, the study was controlled temporally through the pre- vs. post-period design [20–23].

The study was conducted in accordance with the protocol, rules, and regulations of the WCM IRB and standard operating procedures, and sponsor at WCM, and informed consent regulations. Only patients providing informed consent were included in the study. The study followed the hospital's applicable local regulatory requirements, was governed according to local laws and regulations, and was in accordance with the Declaration of Helsinki.

Study Patients

Adult patients (≥ 18 years) admitted to the NYP/WCM hospitalist service with an ABSSSI infection (e.g., diagnosis of cellulitis/erysipelas, wound infection, or major cutaneous abscess) [4, 10, 24] were identified and enrolled based on inclusion and exclusion criteria through patient interview and medical chart review. Enrollment criteria were based on ABSSSI treatment guidelines regarding patients for whom parenteral therapy was indicated because of infection severity, yet could otherwise receive treatment in an outpatient setting [4, 11]. Those with life-

threatening infections, requiring multiple antibiotics or intensive care, or with unstable comorbidities were not eligible (Supplementary Text: Inclusion/Exclusion Criteria).

Follow-up and Outcomes

Patients were followed for 44 days after study enrollment to account for the first 10–14 days of initial ABSSI treatment and for 30 days after treatment; baseline characteristics (Supplementary Text: Study Definitions), health resource utilization, patient-reported outcomes, response to treatment, and adverse events (AEs) were captured (Table S1). Baseline characteristics were collected before patient enrollment in the study at the screening visit and were based on physical examination, patient interview, and medical chart review. Follow-up visits were scheduled between 48 and 72 h after hospital discharge, 10–14 days after enrollment (end of treatment visit), and 44 days after enrollment. Health resource utilization through patient interviews and medical chart review as well as patient-reported outcomes was captured through follow-up visits at 10–14 days and 44 days. Response to treatment was determined by patient interview and examination at 48–72 h and visits at 10–14 days. Safety monitoring was conducted at each visit through the 44-day follow-up period.

Baseline characteristics included demographics, comorbidities, Charlson Comorbidity Index, infection type, infection and clinical characteristics, and utilization of the healthcare service within the past 3 months. The primary outcome was infection-related LOS. Secondary outcomes included other healthcare resource utilization during follow-up, such as all-cause LOS, all-cause 30-day re-admissions, ED visits, and outpatient visits, patient-reported outcomes, response to treatment, and AEs. Patient-reported outcomes including quality of life and work productivity were collected through validated questionnaires (Health-Related Quality-of-Life Medical Outcomes Study Short Form-12 [SF-12] [25], Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 [WPAI:SHP]) [26]. Patient

satisfaction with care was captured using a descriptive survey developed for use in this study. These questionnaires are included in Supplementary Text: Patient Satisfaction Survey.

Statistical Methods

We hypothesized that administration of dalbavancin, a long-acting lipoglycopeptide, in the post-period would decrease LOS and facilitate discharge for eligible patients vs. patients who received usual care in the pre-period. Sample size was determined through a power calculation; with 80% power, a sample size of 86 patients (43 patients per period) supported a decrease in LOS of 2 days in the post-period vs. the pre-period. Outcomes were calculated for the analysis sample, which was defined as all enrolled patients who received ≥ 1 antibiotic dose in the pre-period or one dose of dalbavancin in the post-period. Descriptive statistics, including continuous and categorical variables, were reported for all outcomes. Two-sided Student's *t* tests were used for applicable continuous variables, and Mann-Whitney *U* tests were used if the event normality assumptions were not met. For categorical variables, periods were compared using Chi-squared tests or Fisher's exact tests, as appropriate. All statistical testing applied a significance level of 0.05.

Primary LOS outcome was compared between periods through a two-sided *t* test. To account for baseline differences in characteristics between periods, a generalized linear mixed model was also used in an adjusted analysis using a negative binomial distribution with a log link. The final multivariable model was created through stepwise selection and a statistical significance threshold of $\alpha < 0.1$ for clinically relevant variables specified a priori (Table S2). The final model was adjusted for age and immunocompromised status.

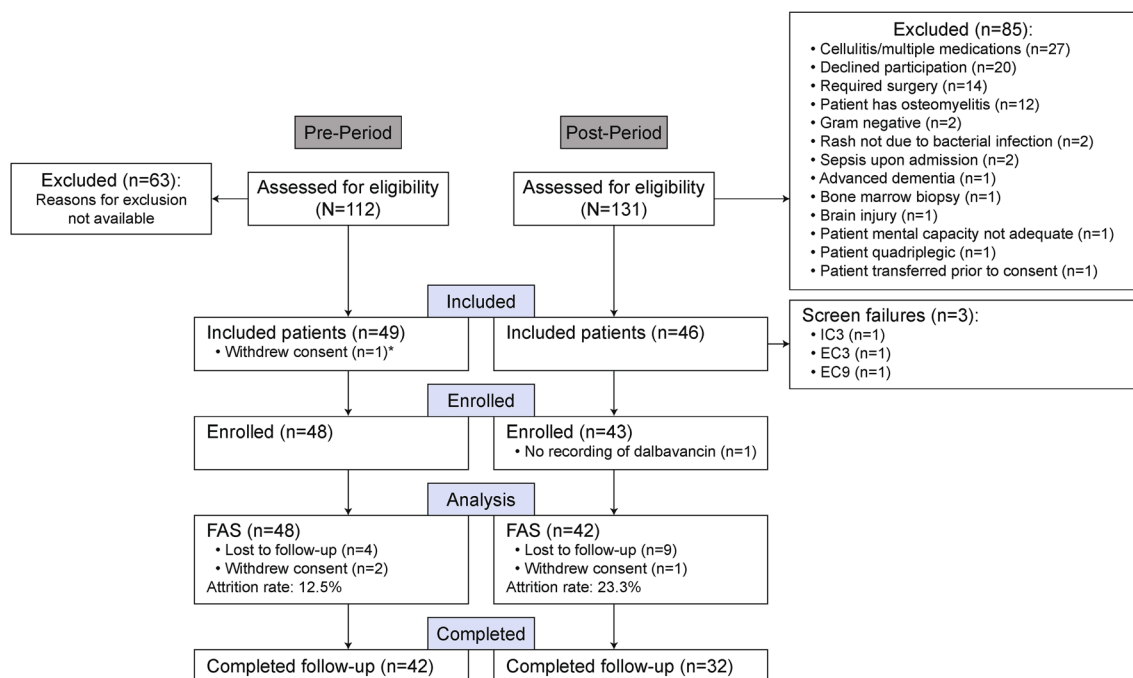


Fig. 1 Patient disposition. *Patient 2010047 provided informed consent for the study, but withdrew it shortly thereafter. Due to timing of consent withdrawal, the patient was removed from the study database. EC3: Known or suspected infections that are severe, life-threatening, or not included in the ABSSI FDA guidance, including the following examples: gangrene; known or suspected necrotizing fasciitis; known or suspected

osteomyelitis, septic arthritis, or endocarditis; diabetic foot infection; and decubitus or ischemic ulcer. EC9: Unwilling or unable to follow study procedures. IC3: Willing and able to return to the hospital or a designated clinic for scheduled visits, or be in contact with the study coordinator through telephone communication, as required by the protocol and the antibiotic treatment administered

RESULTS

Patient Demographics and Disease Characteristics

Among 112 patients screened, 48 patients were enrolled in the pre-period (July 2017–November 2017). During the post-period, among 131 patients screened, 43 patients were enrolled in the post-period from February 2018 to September 2018 (Fig. 1). The attrition rate was 12.5% and 23.3% in the pre- and post-periods, respectively, where loss to follow-up was the primary reason for study withdrawal for both periods. From the enrolled set, one patient from the post-period was not included in the analysis sample as they did not receive ≥ 1 dose of antibiotics after enrollment; therefore, 48 patients in the pre-period and 42 patients in the

post-period were included in the analysis of study outcomes.

Demographics and baseline characteristics were largely similar between groups (Table 1). The majority of patients were admitted from a private home or an independent living facility in the pre-period ($n = 48$; 100%) and post-period ($n = 36$; 85.7%). More patients in the pre-period were unemployed (83%) vs. post-period (52%).

Disease characteristics and medical history were similar between groups (Table 1). Systemic inflammatory response syndrome criteria were met in 11 (22.9%) patients of the pre-period and 8 (19.0%) patients of the post-period. The mean (standard deviation)/median primary lesion size in the pre-period was 533.5 (647.9)/255 cm² and in the post-period was 685.0 (703.5)/458 cm². One patient in the pre-period and two patients

Table 1 Patient demographics and disease characteristics

Characteristics	Pre-period (<i>N</i> = 48)	Post-period (<i>N</i> = 42)	<i>P</i> values
Male, <i>n</i> (%)	24 (50.0)	22 (52.4)	> 0.99
Mean (SD) age, years	59.0 (21.8)	53.4 (21.5)	0.22
Ethnicity, <i>n</i> (%)			
Not Hispanic/Latino	38 (79.2)	26 (61.9)	0.23
Hispanic/Latino	7 (14.6)	8 (19.0)	
Other	3 (6.2)	8 (19.0)	
Race, <i>n</i> (%)			
White	36 (75.0)	28 (66.7)	0.05
Black	1 (2.1)	7 (16.7)	
Asian	1 (2.1)	1 (2.4)	
Other	10 (20.8)	6 (14.3)	
Mean (SD) BMI, kg/m ²	30.2 (8.5)	31.8 (12.4)	0.46
Unemployed	40 (83.3)	22 (52.4)	< 0.001
Admitted to hospital from location, <i>n</i> (%)			
Private home/independent senior living facility	48 (100)	36 (85.7)	0.004
Long-term care or skilled nursing facility, nursing home or rehab facility	0	3 (7.1)	
Other	0	3 (7.1)	
Primary insurance, <i>n</i> (%)			
Government funded	31 (64.6)	22 (52.4)	0.03
Private commercial plan	13 (27.1)	20 (47.6)	
Uninsured	4 (8.3)	0	
Infection type, <i>n</i> (%)			
Cellulitis/erysipelas	41 (85.4)	37 (88.1)	0.71
Wound infection	8 (16.7)	4 (9.5)	0.32
Abscess	1 (2.1)	3 (7.1)	0.34
Purulent drainage from primary lesion, <i>n</i> (%)	13 (27.1)	9 (21.4)	0.53
Mean (SD) primary lesion size, cm ²	533.5 (647.9)	685.0 (703.5)	0.29
Fever, <i>n</i> (%)	4 (8.3)	1 (2.4)	0.37
SIRS criteria met (≥ 2 criteria present), <i>n</i> (%)	11 (22.9)	8 (19.0)	0.65
Recurrent/ABSSSI infection in prior 6 months, <i>n</i> (%)	1 (2.1)	2 (4.8)	0.60
Comorbid conditions, <i>n</i> (%)			
Solid tumor	13 (27.1)	7 (16.7)	0.22

Table 1 continued

Characteristics	Pre-period (<i>N</i> = 48)	Post-period (<i>N</i> = 42)	<i>P</i> values
Moderate to severe chronic kidney disease	10 (20.8)	4 (9.5)	0.13
Peptic ulcer disease	6 (12.5)	3 (7.1)	0.38
Diabetes mellitus	5 (10.4)	6 (14.3)	0.61
Cerebrovascular disease	4 (8.3)	2 (4.8)	0.49
Liver disease	4 (8.3)	0	0.05
Myocardial infarction	3 (6.3)	6 (14.3)	0.13
Peripheral vascular disease	2 (4.2)	2 (4.8)	0.56
Chronic obstructive pulmonary disease	2 (4.2)	0	0.18
Connective tissue disease	1 (2.1)	2 (4.8)	0.50
Leukemia	1 (2.1)	0	0.35
Congestive heart failure	0	1 (2.4)	0.13
Other medical history, <i>n</i> (%)			
Drug abuse	5 (10.4)	3 (7.1)	
Lymphedema	3 (6.3)	3 (7.1)	0.89
Alcohol abuse	0	1 (2.4)	0.29

ABSSSI acute bacterial skin and skin structure infections, *BMI* body mass index, *ED* emergency department, *SIRS* systemic inflammatory response syndrome, *SD* standard deviation

Table 2 Primary outcome over follow-up

Outcomes	Pre-period (<i>N</i> = 48)	Post-period (<i>N</i> = 42)		
Unadjusted total infection-related LOS (days)			Difference (SD)	<i>P</i> value ^a
Mean (SD)	4.8 (2.5)	3.2 (2.5)	1.6 (2.5)	0.003
Median (Q1, Q3)	4.0 (3.0, 5.5)	3.0 (2.0, 3.0)		
Min, max	2.0, 15.0	1.0, 15.0		
95% CI	4.1, 5.6	2.4, 4.0		
Adjusted ^b total infection-related LOS (days)			Difference (SE)	<i>P</i> value ^c
Mean (SE)	5.5 (0.4)	3.9 (0.4)	1.6 (0.5)	0.002

95% CI, 95% confidence interval; LOS, length of stay; Q1, 25th percentile; Q3, 75th percentile; SE, standard error; SD, standard deviation

^a *P* values from a two-sided, two-sample, equal variance *t* test for the unadjusted analysis

^b Generalized linear mixed model assessing the effect of treatment period on total infection-related length of stay (days) by treatment period adjusting for age, and immunocompromised status (patients were defined as immunocompromised if they had evidence of any of the following at baseline: connective tissue disease, diabetes mellitus, leukemia, or malignant lymphoma)

^c *P* values from a two-sided, two-sample, equal variance *t* test for the adjusted analysis

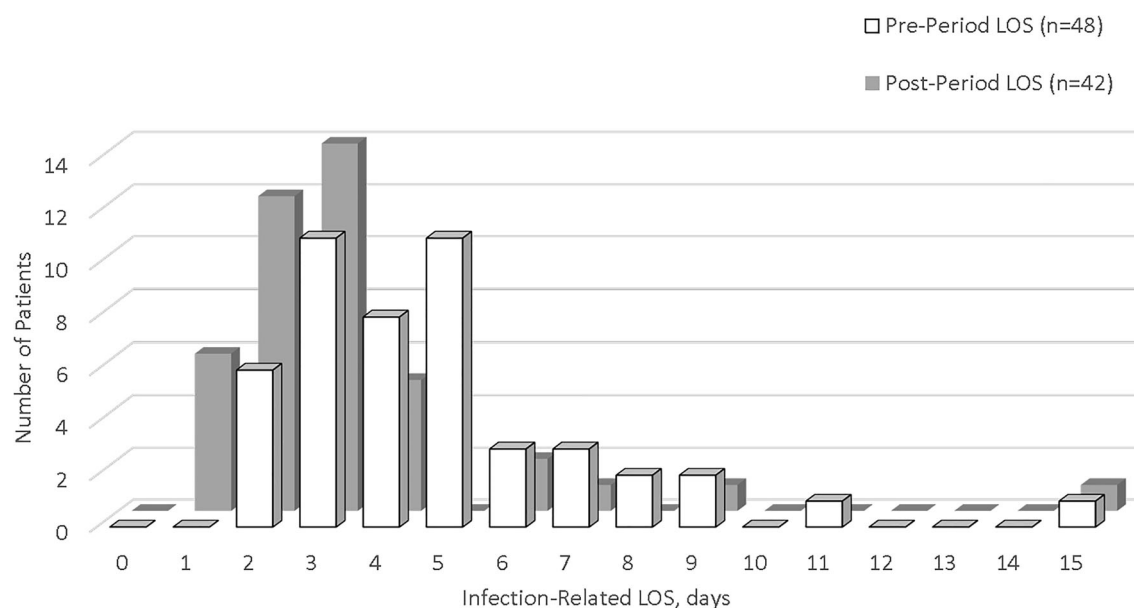


Fig. 2 Histogram of infection-related length of stay. *LOS* length of stay

in the post-period had evidence of a recurrent ABSSSI infection in the prior 6 months.

Antibiotic Treatment Received

In the pre-period group, most patients (66.7%) received multiple antibiotic therapies, with 17.8% of patients receiving > 4 antibiotics. In contrast, most patients (85.7%) received one antibiotic (i.e., dalbavancin) in the post-period. Oral (85.4%) and IV (58.3%) antibiotics were used in the pre-period group, while IV antibiotics were the predominant administration route in the post-period group (100%). Among patients with a reported oral administration route, the majority (64.4%) received oral and IV antibiotics. Moreover, among the pre-period group, 87.5% of patients completed their initial antibiotic treatments compared with 100% in the post-period group.

Effects on LOS

A significant reduction in mean infection-related LOS was supported in the post- vs. pre-period (3.2 days vs. 4.8 days; $P = 0.003$) (Table 2; Fig. 2). All-cause LOS was also significantly reduced (3.2 days vs. 4.9 days; $P = 0.003$).

Table 3 Health resource utilization outcomes over follow-up

Outcomes	Pre-period (<i>N</i> = 48)	Post-period (<i>N</i> = 42)
Health resource utilization, <i>n</i> (%)		
Infection-related major surgical intervention that required OR time	0	1 (2.4)
All-cause hospitalization in the 30 days following discharge	1 (2.1)	3 (7.1)
Infection-related hospitalizations during follow-up	0	2 (4.8)
Infection-related hospitalizations during follow-up that required ICU admissions	0	0

OR operating room, *ICU* intensive care unit

Table 4 Other outcomes over follow-up

Outcomes	Pre-period (<i>N</i> = 48)	Post-period (<i>N</i> = 42)	<i>P</i> value
Work productivity and activity impairment, % (95% CI) at day 14 visit ^a			
Absenteeism	<i>n</i> = 17 49.9 (30.1, 69.7)	<i>n</i> = 16 36.7 (12.2, 61.3)	0.38
Impairment while working	<i>n</i> = 14 47.9 (24.7, 71.0)	<i>n</i> = 9 8.9 (1.8, 16.0)	0.01
Overall work impairment	<i>n</i> = 14 59.3 (36.7, 81.9)	<i>n</i> = 9 18.0 (0.0, 36.0)	0.01
Activity Impairment (non-work related)	<i>n</i> = 42 60.2 (48.1, 72.3)	<i>n</i> = 33 18.5 (9.2, 27.8)	< 0.001
Quality of life (mean, SD) ^a			
SF-12 MCS at baseline	<i>n</i> = 47 42.9 (10.5)	<i>n</i> = 42 49.2 (11.9)	0.85
SF-12 MCS at day 14 visit	<i>n</i> = 42 43.9 (10.2) ^b	<i>n</i> = 34 50.8 (10.9) ^c	
SF-12 PCS at baseline	<i>n</i> = 47 36.8 (9.6)	<i>n</i> = 42 37.6 (10.7)	0.07
SF-12 PCS at day 14 visit	<i>n</i> = 42 40.5 (11.4) ^b	<i>n</i> = 34 46.3 (11.2) ^c	
Response to treatment (<i>n</i> , %) at day 14 visit ^a			
Complete response	24 (50.0)	24 (57.1)	0.58
Partial response	0 (0)	0 (0)	
Failure	12 (25.0)	9 (21.4)	
Unknown	12 (25.0)	9 (21.4)	
Adverse events			
Adverse events, <i>n</i> (%)	3 (6.3)	20 (47.6)	
Severity of AEs ^{d,e}			
Mild	0 (0)	15 (35.7)	
Moderate	3 (6.3)	4 (9.5)	
Severe	0 (0)	1 (2.4)	
AEs with possible causal relationship to study drug ^{d,e}			
Mild	0 (0)	6 (14.3)	
Moderate	0 (0)	2 (4.8)	
Severe	0 (0)	0 (0)	

Table 4 continued

Outcomes	Pre-period (<i>N</i> = 48)	Post-period (<i>N</i> = 42)	<i>P</i> value
AEs leading to study discontinuation	0	0	
AEs leading to death	0	0	
Serious adverse events	1 (2.1)	3 (7.1)	

95% CI 95% confidence interval, AE adverse event, MCS mental health composite scale, PCS physical health composite scale, SD standard deviation, SF-12 short form 12

^a Not all data from patients in the analysis sample were available because of loss to follow-up or incomplete data at baseline and/or day 14 visit

^b Change from baseline to day 14 for MCS and PCS nonsignificant in the pre-period

^c Change from baseline to day 14 for MCS non-significant, yet PCS significant ($P < 0.001$) in the post-period

^d Percentages of severity of adverse events were derived from patients who received study drug

^e Patients may have had more than one event

Similar results were found after infection-related LOS was adjusted for age and immunocompromised status (3.9 days vs. 5.5 days; $P = 0.002$).

Half of all patients from the post-period group (21 patients, 50%) were discharged to complete care in an outpatient setting on the same day dalbavancin was provided. Of the 50% who were not discharged on the same day, the most common reasons were due to additional monitoring/procedures for ABSSSI (10 patients; 47.6%) or non-ABSSSI reasons (9 patients; 42.9%).

Effect on Other Health Resource Utilization

No major surgical interventions occurred during pre-period follow-up; one was identified during post-period follow-up for non-ABSSSI care (breast reconstruction). All-cause hospitalization in the 30 days after discharge was numerically higher in the post- vs. the pre-period ($n = 3$ vs. $n = 1$). During follow-up, no patient from the pre-period group and two patients from the post-period group were re-hospitalized because of the index ABSSSI. Over the entire study duration, no infection-related hospitalization resulted in admission to ICU in either group (Table 3).

Effects on Patient-reported Outcomes

Although fewer than half of the patients responded, the work productivity and activity impairment (impairment while working, overall work impairment, and non-work related impairment of activity) outcomes significantly improved in the post-period ($P \leq 0.01$) (Table 4). Absenteeism and quality of life outcomes were not significantly different between the pre- and post-periods.

A smaller proportion of patients in the pre-period group expressed no concern about receiving an IV therapy compared with patients in the post-period group (Table 5; 54.8% vs. 78.8%). If they were treated again for a similar ABSSSI, patients from both groups preferred (65.1% and 97.1%, respectively) receiving one single dose of an IV antibiotic. Most patients would find value in a physician who recommended that they receive an IV antibiotic therapy that might shorten their hospital LOS.

Therapeutic Response

The percentage of patients with complete treatment response was similar between periods (50.0% in the pre-period and 57.1% in the post-period; Table 4).

Table 5 Patient satisfaction survey results

	Pre-period (<i>N</i> = 48)	Post-period (<i>N</i> = 42)
Number of patients with any survey data, <i>n</i> (%)	43 (89.6)	34 (81.0)
Number of patients with all survey questions completed, <i>n</i> (%)	40 (83.3)	32 (76.2)
Concerned about receiving your IV therapy, <i>n</i> (%)		
None of the time	23 (54.8)	26 (78.8)
A little of the time	13 (31.0)	4 (12.1)
Some of the time	3 (7.1)	1 (3.0)
Most of the time	1 (2.4)	1 (3.0)
All of the time	2 (4.8)	1 (3.0)
Regimen preferred if treated again for a similar skin infection with IV, <i>n</i> (%)		
One single IV antibiotic dose to complete your course of treatment	28 (65.1)	33 (97.1)
One or two daily IV antibiotic doses every day for 7–14 days to complete your course of treatment	6 (14.0)	0 (0.0)
One or two daily IV antibiotic doses for a few days, then oral antibiotics three or four times per day for the remaining 7–14 days course of treatment	9 (20.9)	1 (2.9)
Time willing to spend receiving each IV, <i>n</i> (%)		
About 30 min or less	23 (56.1)	22 (64.7)
About 1 h	10 (24.4%)	10 (29.4%)
About 1.5–2 h	5 (12.2%)	1 (2.9%)
About 3 h or longer	3 (7.3%)	1 (2.9%)
Find value in a physician who recommended that you receive an IV antibiotic therapy that may shorten your hospital length of stay, <i>n</i> (%)		
Definitely not	1 (2.3%)	1 (2.9%)
Probably not	1 (2.3%)	1 (2.9%)
Probably so	7 (16.3%)	2 (5.9%)
Definitely so	34 (79.1%)	30 (88.2%)

Adverse Events

Among AEs identified, 16.7% (*n* = 7) were found to have a possible causal relation to a study drug in the post-period. A greater proportion of AEs occurred in the post-period (*n* = 20; 47.6%) vs. pre-period (*n* = 3; 6.3%) with most AEs being mild in severity and not related to antibiotic use; few AEs were serious (7.1% post-period vs.

2.1% pre-period) (Table 4). One of the serious AEs (vomiting) was considered to be probably related to the study drug; it was mild in severity and occurred 2 h after dalbavancin treatment for a patient in the post-period. The most common AEs were unrelated infection in the pre-period and fever in the post-period.

DISCUSSION

As hospitals are under pressure to improve quality of care, a critical evaluation of current pathways and processes is warranted. Admission to the hospitalist service for ABSSSI imposes a significant economic burden on the US health system, with hospital LOS as a key cost driver [5, 6, 12, 27–29]. We found that LOS was ~ 5 days on average in our study for those patients in the pre-period vs. the post-period LOS of ~ 3 days. Due to the increasing emphasis on efficiency and quality of care, the development of new ABSSSI care pathways that improve hospital efficiency and reduce the costs associated with unnecessary or prolonged hospital admissions is warranted [4, 9–12]. A key component of a new care pathway may leverage long-acting antibiotic therapy, such as dalbavancin. Yet, it is necessary to not only support process improvements, but also to establish the safety and efficacy of new care pathways in a real-world setting.

Our study is the first pragmatic clinical trial to date to implement use of a long-acting antibiotic, dalbavancin, for ABSSSI treatment among admitted patients on a hospitalist service in a large hospital setting. Following implementation of dalbavancin treatment in this real-world study, infection-related hospital LOS and overall LOS were significantly decreased by nearly 2 days. Additional health resource utilization, indicative of poor outcomes or the need for follow-up care, such as 30-day hospitalization rates, use of the intensive care unit, and ED and outpatient visits, was found to be similar between periods. As patient satisfaction is of increasing importance in measuring quality of care [18], patient-reported work or activity impairment were also significantly reduced in patients in the post- vs. pre-period. Patients in the post-period reported similar health related quality of life and patient satisfaction. Our results were similar to prior patient preference research [8] in that the majority of patients preferred antibiotic regimens similar to dalbavancin (i.e., single dose, shorter infusion durations) over other options, and most would find value in a physician who

provided an option that could shorten their hospital LOS. This latter option is likely linked to the improved patient-reported indices of work productivity. It should be noted, however, that there was a higher attrition rate and a higher percentage of patients readmitted to the hospital in the post-period. These cases included individuals with concomitant medical conditions requiring further care and did not represent antimicrobial treatment failure for ABSSSI.

In addition to increasing quality and efficiency of care, ensuring the response to treatment and safety profile of the dalbavancin pathway is paramount. Response to treatment was similar between the treatment groups. As a more clinically meaningful measure of safety versus AEs overall, 16.7% ($n = 7$) of AEs were found to have a possible causal relation to dalbavancin in the post-period. The number of AEs in patients within the post-period were higher vs. the pre-period, while serious AEs were similar between periods. Moreover, no patients discontinued treatment, and mortality did not occur in either period. The AEs were largely unrelated to the infection being treated or due to known toxicities of dalbavancin [30]. The more involved informed consent process in the post-period versus the pre-period (observational design) may have contributed to difference in AEs between periods. These measures support our hypothesis that ENHANCE may be an effective alternative care pathway.

Our research builds on prior evidence that dalbavancin is a safe, effective [30–32], and potentially cost-saving option for outpatient ABSSSI treatment [33]. Outpatient treatment has been shown to result in reduced hospital stay resulting in lower costs [5, 12, 27, 29], highlighting the importance of alternative treatment options. Indeed, the estimated cost of a day in a non-profit hospital located in New York (similar to the characteristics of NYP/WCM) is approximately \$2719 [34]. Considering LOS for ENHANCE post-period patients was reduced by 1.6 days, the estimated savings would partially or fully offset the cost of long-acting antibiotic therapy, such as dalbavancin. Such an estimate does not take into account the

costs of pharmacy and nursing for administration.

Despite the higher acquisition cost of dalbavancin one could hypothesize that the reduced LOS, increased work activity, and reduction in the use of multiple inpatient antibiotics could lead to significant cost savings. We also suggest that a registry of the use of dalbavancin be implemented in those institutions adapting the ENHANCE ABSSSI pathway to prospectively monitor the impact of this strategy.

Although a potential limitation of the study might be the single-center design, this design feature eliminated variability that could occur in a study involving multiple hospitals, such as number of hospital staff, staffing hours, etc. However, it may limit the generalizability of our findings. A prospective multicenter registry could be implemented to validate this approach to management of patients hospitalized with ABSSSI. Another limitation was lack of randomization in this study, which could bias results because of differences between pre- and post-period patients at baseline. Yet, our study was consistent with real-world clinical practices, as randomization of patients or hospitals to receive different clinical pathways is not always feasible, and we found similar baseline characteristics between both periods [23]. Consistent with other studies, we observed a seasonality to ABSSSI (i.e., infections were more prevalent during the summer months). Although randomization at the level of the patient or site was not implemented, the pre-period of the study served as an observational control group, supporting a controlled trial design. We acknowledge that selection bias is an important factor that can impact study design; however, we believe that selection criteria were similarly applied in each study period through consistently implemented site training.

CONCLUSION

In summary, the ENHANCE ABSSSI pathway among eligible patients on a hospitalist service significantly reduced LOS by 1.6 days with

improvements in work productivity and the ability to complete daily activities.

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Compliance with Ethics Guidelines. The study was conducted in accordance with the protocol, rules, and regulations of the WCM IRB and standard operating procedures, and sponsor at WCM, and informed consent regulations. Only patients providing informed consent were included in the study. The study followed the hospital's applicable local regulatory requirements, was governed according to local laws and regulations and was in accordance with the Declaration of Helsinki.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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