Hospital Avoidance Strategies for Treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

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A Introduction

A1 Study Abstract

More than 40% of patients presenting with acute bacterial skin and skin structure infection (ABSSSI) to the Barnes-Jewish Hospital (BJH) emergency department (ED) are admitted for intravenous antibiotics. There is growing evidence to suggest that many hospital admissions for uncomplicated ABSSSI due to Gram-positive bacteria could be avoided with an alternative treatment strategy employing newer long-acting antibiotics. Coupled with close outpatient follow-up, such an alternative hospital avoidance strategy has the potential to improve quality and value of care for patients with uncomplicated ABSSSI and optimize use of limited inpatient healthcare resources.

A2 Primary Hypothesis

Patients with uncomplicated ABSSSI suspected to be due to Gram-positive bacteria treated using an alternative strategy consisting of single-dose dalbavancin and close outpatient follow-up will have lower healthcare service utilization, lower healthcare-associated costs, greater patient satisfaction, and comparable safety compared to "usual care" (hospital admission for intravenous antibiotics) at BJH.

A3 Purpose of the Study Protocol

Conduct a single center, randomized controlled study to compare healthcare service utilization, healthcare-associated costs, patient satisfaction, patient safety, and clinical outcomes in BJH ED patients with uncomplicated ABSSSI suspected to be due to Gram-positive bacteria treated with single-dose dalbavancin (alternative strategy) *vs.* hospital admission for intravenous antibiotics ("usual care").

B Background

B1 Prior Literature and Studies

Acute bacterial skin and skin structure infections (ABSSSI), including cellulitis, erysipelas, wound infections, and major cutaneous abscesses, are routinely treated in the emergency department (ED). Cellulitis ranks third behind only *chest pain* and *asthm*a as the most common reason patients seek care in the ED. Nationwide, nearly 20% of ABSSSI patients evaluated in EDs are admitted to the hospital to receive intravenous antimicrobial therapy, contributing 870,000 hospital admissions a year at a cost of more than $6 billion in charges annually [1]. While hospital admission is necessary for patients with life-threatening infection, significant medical comorbidities, or other concurrent acute illness, mounting evidence suggests that **a substantial number of ABSSSI patients are unnecessarily admitted or are admitted for longer than**

necessary durations to receive intravenous antimicrobial therapy [2]. If we consider that the average national inpatient length of stay for cellulitis (the most common form of ABSSSI) is 3.97 days at an average cost of more than $6,000 per patient, it becomes clear that the management of ABSSSI currently utilizes significant inpatient healthcare resources. Decisions to admit or discharge a patient with ABSSSI in the ED are often based on physician preference, which may be influenced by patient expectations as well as the perceived likelihood of whether the patient will adhere to outpatient antimicrobial therapy and/or complete timely follow-up in the ambulatory setting. **Novel alternative treatment strategies focused on hospital admission avoidance taking into account these practical considerations have the potential to improve the quality and value of care for patients presenting to the ED with uncomplicated ABSSSI.**

While vancomycin is most frequently used in the ED and inpatient setting to empirically treat ABSSSI suspected to be caused by Gram-positive bacteria (*e.g.*, methicillin-sensitive and -resistant *Staphylococcus aureus*, *Streptococcus pyogenes, Enterococcus faecalis*), this antibiotic must be administered multiple times at regular intervals over a course of therapy through an intravenous catheter. Challenges achieving and maintaining therapeutic serum drug levels coupled with the potential for renal toxicity and catheter-associated bloodstream infections can adversely impact patient care.

Dalbavancin, a novel lipoglycopeptide antibiotic, has been approved by the FDA for the treatment of ABSSSI caused by Gram-positive bacteria. Once-weekly intravenous dalbavancin has been shown to be non-inferior to twice-daily intravenous vancomycin followed by oral linezolid for treatment of ABSSSI over a 10-14 day course of therapy [3]. Furthermore, a single 1500 mg infusion of dalbavancin has been demonstrated to be non-inferior to a 2-dose regimen for treatment of ABSSSI with comparable safety profile [4]. The extended half-life of dalbavancin therefore allows for an effective treatment course of >7 days with a single dose, the accepted duration of therapy for uncomplicated ABSSSI. Dalbavancin is currently being used in clinical practice across the U.S. to treat ABSSSI.

B2 Rationale for this Study

At Barnes-Jewish Hospital (BJH), almost 40% of the more than 200 ABSSSI patients evaluated monthly in our ED are admitted for inpatient antibiotic therapy. Close collaborations between the Divisions of Emergency Medicine and Infectious Diseases at Washington University School of Medicine provide a robust infrastructure to implement and study an alternative treatment strategy incorporating single-dose administration of dalbavancin in the ED followed by close outpatient follow-up in the Washington University Infectious Disease Clinic.

We believe that such an approach will conserve hospital resources by reducing admissions for uncomplicated ABSSSI while delivering comparable if not superior care for this disease, allowing optimal utilization of BJH inpatient beds for other serious medical conditions requiring inpatient care. We believe this novel alternative approach will allow hospitals such as BJH to more cost-effectively and efficiently manage ABSSSI patients. This study will reduce the number of >2 midnight observation admissions to BJH for ABSSSI, thereby improving inpatient capacity to care for patients requiring >2 midnight hospital inpatient admission.

C Study Objectives

C1 Primary Aim

Implement a study protocol within the BJH ED to treat uncomplicated ABSSSI patients comparing a novel alternative treatment strategy (single-dose intravenous dalbavancin) with close outpatient follow-up *vs.* "usual care" (hospital admission for multiple doses of intravenous antibiotic) with relation to the following outcomes:

- Healthcare service utilization (*e.g.*, ED length-of-stay, inpatient length-of-stay, ED revisits, need for inpatient admission/readmission)
- Healthcare-associated costs
- Patient satisfaction [including completion of items from the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey and a targeted set of questions specific to ABSSSI care]
- Patient safety (*e.g.*, adverse drug events, laboratory testing for drug-associated toxicity)
- Clinical outcomes (*e.g.*, change in size of ABSSSI lesion, resolution of symptoms, need for additional intravenous/oral antibiotic therapy)

C2 Rationale for the Selection of Outcome Measures

Existing data on healthcare service utilization and cost related to the use of new long-acting antibiotics to treat uncomplicated ABSSSI are limited to economic modeling [5-7]. Real-world data describing these outcomes from a randomized, controlled study do not exist to the best of our knowledge. Likewise, little if any data exists comparing patient satisfaction between those receiving long-acting antibiotics vs. usual care. Patient safety and clinical outcomes data have been reported in previous large randomized controlled trials [3, 4].

D Study Design

D1 Overview or Design Summary

This study will be single center, randomized, non-blinded study comparing two active treatment arms to treat uncomplicated ABSSSI suspected to be due to Gram-positive bacteria:

- Alternative treatment strategy comprised of a single dose of dalbavancin administered in the BJH ED or ED observation unit followed by discharge w/ close Infectious Disease outpatient clinic follow-up

  vs.
- "Usual care" (*i.e.*, hospital admission for intravenous antibiotics – typically, vancomycin) – antibiotic and doses to be determined at the discretion of the treating clinician (both in the BJH ED and on the BJH inpatient ward)

Initial patient recruitment, randomization, and data collection (including patient demographics, clinical measures, physical examination, adverse drug monitoring, patient satisfaction) will be

conducted by research coordinators and faculty from the Washington University Emergency Care Research Core (ECRC) while the patient is in the BJH ED on Day 1. Patients in the "usual care" arm will continue to be followed by the ECRC during their inpatient hospital stay.

Patients in the alternative treatment strategy arm discharged from the BJH ED will receive in-person outpatient follow-up (including assessment of clinical measures, adverse drug monitoring, patient satisfaction) in the Washington University Infectious Disease Clinic (specifically the Infectious Disease Clinical Research Unit, or ID-CRU, co-located within the Infectious Disease Clinic) between Day 3 and Day 7. This in-person follow-up will be conducted by an infectious disease specialist (either the PI or sub-PI) in concert with research coordinators from the ID-CRU. Telephone follow-up for these patients focusing on healthcare utilization and patient satisfaction will occur at Day 14 and Day 28.

Patients in the "usual care" arm will receive in-person follow-up during their hospital admission or in the ID-CRU between Day 3 and Day 7, with the same evaluation as the alternative treatment strategy arm. Telephone follow-up will likewise occur at Day 14 and Day 28.

Additional information on study outcome measures related to management of their uncomplicated ABSSSI through Day 28 will be obtained from review of patient electronic health records and BJH healthcare cost/financial data.

D2 Subject Selection and Withdrawal

2.a Inclusion Criteria

- Adult (age ≥18 years)
- Diagnosis of uncomplicated ABSSSI suspected to be due to Gram-positive bacteria by treating ED clinician, with presence of the following:
    - Skin lesion size ≥75 cm^2 (measured by area of erythema, edema, and/or induration)
      AND
    - Signs of systemic inflammation (at least 1 of the following: WBC >12,000 or <4,000 cells/mm^3; ≥10% immature neutrophils on peripheral smear; temperature >38.3˚C or <36˚C; heart rate >90 bpm, respiratory rate >20 bpm). Signs of systemic inflammation not required if the patient is age >70 years, has diabetes mellitus, or has been treated with immunosuppressive or chemotherapy in the past 90 days.
- Clinical determination by treating ED clinician that patient will need hospital admission for the sole purpose of receiving intravenous antibiotics directed only towards Gram-positive bacteria (*e.g.*, vancomycin, cefazolin) to treat uncomplicated ABSSSI

2.a Exclusion Criteria

- Risk for ABSSSI due to Gram-negative bacteria (neutropenia with absolute neutrophil count <500 cells/µL, HIV or severely immunocompromised, burns, infection after trauma or as a result of an aquatic environment, infection after skin graft)
- Any abscess requiring operative drainage

- Infection due to a vascular catheter or prosthetic device
- Infection of a diabetic foot ulcer or decubitus ulcer
- Necrotizing soft tissue infection
- Sepsis (quick SOFA score ≥2) or septic shock (requiring vasopressors to maintain mean arterial pressure ≥65 mmHg despite resuscitation with at least 30mL/kg of IV crystalloid within first 3 hours)
- Hypersensitivity to glycopeptides (vancomycin, televancin, dalbavancin, oritavancin)
- Severe renal insufficiency (CrCl <30 mL/min)
- Severe hepatic insufficiency (Child-Pugh Class C)
- Pregnant or nursing

2.b Ethical Considerations

Dalbvancin has been approved by the FDA for the treatment of ABSSSI due to Gram-positive bacteria and is currently being used in clinical practice in the U.S. Therefore, both the alternative treatment strategy and “usual care” strategy represent accepted medical therapies to treat ABSSSI.

2.c Subject Recruitment Plans and Consent Process

All patients approached for participation in the study will have a diagnosis or clinical impression made by the treating ED clinician of uncomplicated ABSSSI suspected to be due to Gram-positive bacteria requiring intravenous antimicrobial therapy and hospital admission for this sole purpose. The patient will be approached for participation in the ED treatment room to maintain privacy to discuss the study. The investigators will discuss with the patient that there is a study being conducted in the BJH ED that they may qualify for that involves using either a single dose of a new FDA-approved long-acting antibiotic (dalbavancin) followed by discharge home or admission to the hospital for "usual care" (multiple doses of intravenous antibiotics). They will be informed that the newer long-acting antibiotics have been found to be non-inferior to "usual care" in the treatment of ABSSSI. Patients will be informed about the potential side effects they may experience by receiving these medications. Patients randomized to receive dalbavancin will be told that they may opt out of the study at any point in time if they think they are not getting appropriate treatment for their ABSSSI, defaulting to hospital admission for "usual care".

2.d Randomization Method and Blinding

Patients will be randomized using a random number generator. Patients with an odd number will receive the single-dose long-acting antibiotic, dalbavancin, in the BJH ED. Those with an even number will receive “usual care” with intermittent intravenous antibiotics at the discretion of the treating ED clinician and inpatient physician upon hospital admission. This study will not involve blinding.

2.e Risks and Benefits

Patients receiving dalbavancin may be at risk for flushing, headache, rash, nausea, vomiting, diarrhea, or other allergic reaction. Nausea is the most common side effect of dalbavancin and adverse drug events range anywhere from 1-10%.

Vancomycin, a standard antibiotic used to treat most Gram-positive bacterial infections, may cause hypotension, flushing, red man syndrome, phlebitis, rash, or nephrotoxicity in some cases.

The side effects of vancomycin and other standard antibiotics (*e.g.*, cefazolin) are well-known to clinicians given their widespread day-to-day use in the hospital.

For patients receiving dalbavancin, the benefits of participating in the study include avoidance of hospital admission and receipt of this antibiotic at no cost. They will also benefit from frequent clinical monitoring both in the ED and outpatient clinic setting. These patients may also benefit from higher satisfaction and comfort at being able to recover from their illness at home rather than in the hospital, eliminating the need for frequent blood tests, intravenous infusions, and prolonged convalescence in bed, as well as the risk for healthcare-associated infections (e.g., phlebitis, central venous catheter infection, pneumonia). They may also have reduced healthcare costs overall.

Patients receiving "usual care" will have the benefit of longer direct observation in the hospital.

2.f Early Withdrawal of Subjects

Patients may withdraw from the study at any time. Patients who experience an adverse drug event requiring termination of dalbavancin infusion in the ED prior to administration of the full dose will be withdrawn from the study. Patients may opt out of the study at any point in time if they think they are not getting appropriate treatment for their ABSSSI, defaulting to hospital admission for "usual care".

2.g When and How to Withdraw Subjects

Patients and/or family members designated as power of attorney may provide verbal or written notification of their intent to withdraw from the study at any time.

2.h Data Collection and Follow-up for Withdrawn Subjects

No additional data will be collected from patients that have withdrawn from the study.

D3 Study Drug

3.a Description

The study drug, dalbavancin, is a novel lipoglycopeptide that has been approved by the FDA for the treatment of ABSSSI due to Gram-positive bacteria. It will be administered to patients randomized to the alternative treatment strategy arm.

3.b Treatment Regimen

Alternative treatment strategy arm: Single 1500mg intravenous dose of dalbavancin, administered over a 30-minute time period.

"Usual care" arm: Antibiotic selection, duration, and frequency of administration will be decided at the discretion of the treating ED and inpatient care clinician.

3.c Method for Assigning Subjects to Treatment Groups

Random number generator, conducted by the ECRC research coordinator.

3.d Preparation and Administration of Study Drug

Dalbavancin is supplied in single-use vials containing 500mg of the drug in sterile powder form. In accordance with the package insert for dalbavancin, each 500mg vial must be reconstituted with either 25 mL of sterile water for injection, USP, or 5% dextrose injection, USP. After slow addition of either injection, the vial should be gently rolled to ensure all surfaces containing dalbavancin have been wetted. Alternatively, brief, gentle swirling with inversion of the vial can also be performed to dissolve the dalbavancin. Each reconstituted vial will contain 20mg/mL of dalbavancin.

Prior to administration, the reconstituted vial(s) of dalbavancin must be further diluted into a 250mL bag of 5% dextrose for injection, USP, for a final concentration of 1 mg/mL to 5 mg/mL.

Dalbavancin should be administered via intravenous infusion, using a total infusion time of 30 minutes.

Dalbavancin should not be co-infused with other medications or electrolytes. Saline-based infusion solutions may cause precipitation and should not be used. If a common intravenous line is being used to administer other drugs in addition to dalbavancin, the line should be flushed before and after each dalbvancin infusion with 5% dextrose injection, USP.

3.e Subject Compliance Monitoring

Administration of dalbavancin will occur in the BJH ED under the supervision of the research team and treating clinical staff.

3.f Blinding of Study Drug

Blinding of study drug will not be performed in this study.

3.g Receiving, Storage, Dispensing and Return

Dalbavancin doses will be stored in the BJH Research Pharmacy.

When a patient has been identified and randomized to the alternative treatment strategy arm, a single 1500 mg dose of dalbavancin will be reconstituted in and released from the BJH Research Pharmacy to the BJH ED for study patient use.

E Study Procedures

E1 Screening for Eligibility

Patients diagnosed with uncomplicated ABSSSI suspected to be due to Gram-positive bacteria in the BJH ED and felt by the treating clinician to require hospital admission for intravenous antibiotics alone will be approached for participation in the study by ECRC research coordinators. ECRC will use a combination of electronic medical record review and query by CASE-ED (Computer-Assisted Subject Enrollment for the ED) (HRPO #201106074), a software system that automatically captures and screens ED clinical data in the electronic medical record.

E2 Schedule of Measurements

- Day 1 (BJH ED) – in-person
    - Patient demographics (*e.g.*, age, sex, race, payor/insurance status, history of substance dependence, lack of housing)
    - Clinical characteristics (comorbid diseases, prior/current medications including antibiotics, signs/symptoms associated with ABSSSI, measurement of lesion size, Eron severity classification, vital signs, ED laboratory data)
    - Adverse drug events associated with antibiotic(s) received in the BJH ED
    - Patient satisfaction & quality of life measures

- Day 3 to Day 7 (ID Clinic/ID-CRU or BJH) – in-person
    - Self-reported healthcare utilization
    - Clinical characteristics (signs/symptoms associated with ABSSSI, measurement of lesion size, vital signs)
    - Laboratory blood draw to monitor for drug-associate toxicity (CBC, CMP)
    - Patient satisfaction measures

- Day 14 – via telephone
    - Self-reported healthcare utilization
    - Clinical characteristics (signs/symptoms associated with ABSSSI)
    - Patient satisfaction measures

- Day 28 – via telephone
    - Self-reported healthcare utilization
    - Clinical characteristics (signs/symptoms associated with ABSSSI)
    - Patient satisfaction & quality of life measures

E3 Safety and Adverse Events

3.a Safety and Compliance Monitoring

Antibiotic-related safety and adverse events will be captured on Day 1 in the BJH ED and at in-person follow-up between Day 3 to Day 7 at BJH or in the Infectious Disease Clinic/ID-CRU through patient interview and laboratory testing. Additional assessment will occur by patient interview only on Day 14 and Day 28 via telephone. Potential safety and adverse events include:

- Anaphylaxis
- Infusion-related reaction (*e.g.*, flushing, hypotension, redman's syndrome)
- Milder allergic reaction (*e.g.*, rash)
- Drug side effects (*e.g.*, headache, rash, nausea, vomiting, diarrhea)
- Nephrotoxicity
- Hepatotoxicity

3.b Medical Monitoring

i Investigator only

Safety and adverse events will be monitored regularly and tallied after every 10 patients. If 5 or more events are identified in the alternative treatment strategy arm employing single-dose dalbavancin, an Institutional Data and Safety Monitoring Board will be convened.

ii Institutional Data and Safety Monitoring Board

We have identified 3 independent experts within the Division of Infectious Diseases not involved with the study to form the Institutional Data Safety Monitoring Board for this study. They will be tasked with performing a formal interim analysis of safety and adverse events related to the alternative treatment strategy arm upon request.

3.c Definitions of Adverse Events

An adverse event is defined as any untoward medical occurrence in a study subject administered a medication (investigational or non-investigational). An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medication (investigational or non-investigational), whether or not related to that medication. (definition per International Conference on Harmonisation, ICH) This includes any occurrence that is new in onsent or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Serious adverse event:

A serious adverse event (SAE) based on ICH is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmittion of any infectious agent via a medicinal product
- Is medically important based on medical and scientific judgment

Unlisted (unexpected) adverse event

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information (*e.g.*, package insert).

Adverse event associated with use of the drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probably, or very likely by the relationship definitions listed in Section 3.d.i.

3.d Classification of Events

i Relationship

Not Related
An adverse event that is not related to the use of the drug.

Doubtful
An adverse event for which an alternative explanation is more likely, *e.g.*, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible
An adverse event that might be due to the use of the drug. An alternative explanation, *e.g.*, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable
An adverse event that might be due to the use of the drug. The relationship in time is suggestive (*e.g.*, confirmed by dechallenge). An alternative explanation is less likely, *e.g.*, concomitant drug(s), concomitant disease(s).

Very Likely
An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, *e.g.*, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (*e.g.*, it is confirmed by dechallenge and rechallenge).

ii Severity

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities. The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (*e.g.*, laboratory abnormalities).

iii Expectedness

Adverse drug events associated with dalbavancin may range anywhere from 1-10%, with nausesa being the most common.

3.e Data Collection & Reporting Procedures for Adverse Events

Serious adverse events, including those spontaneously reported to the research team, occuring within 30 days after receiving the single dose of dalbavancin or “usual care” antibiotics will be reported to the Prinicipal Investigator within 24 hours. Any event requiring hospitalization (or

prolongation of hospitalization) that occurs during the course of the patient's participation in the study must be reported as a SAE, except hospitalizations for the following:

- The "usual care" arm of this study will involve hospital admission for intravenous antibiotic therapy. This hospital admission for patients randomized to "usual care" should not be reported as an SAE.
- Hospitalizations not intended to treat an acute illness or adverse event (*e.g.*, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study

Data on SAEs will be collected and reported using an Adverse Event Form.
Unlisted adverse event and any non-serious adverse event associated with the use of the drug will be collected and reported using an Adverse Event Form.

An interim analysis of adverse events will performed after every 10 patients. If we identify 5 or more adverse events possibly related to dalbavancin, we will suspend the study until we can have an Institutional Data and Safety Monitoring Board perform a formal interim analysis to determine if there is a safety issue.

E4 Study Outcome Measurements and Ascertainment

Healthcare utilization related to ABSSSI (at any time between Day 1 and Day 28):

- Repeat ED visit (s)
- Need for hospital admission(s) to receive intravenous antibiotics (excluding initial hospital admission in "usual care" arm)
- Need for switch to a different oral or intravenous antibiotic to treat ABSSSI

Healthcare cost related to ABSSSI management

- Indirect/direct costs associated with ED visit(s) within BJC system
- Indirect/direct costs associated with hospital admission(s) within BJC system

Patient satisfaction & quality of life

- Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey items
- Rand 36-Item Health Survey 1.0 Questionnaire (SF-36)
- Targeted set of questions specific to ABSSSI care and patient-centered outcomes

Patient safety

- Adverse drug events
- Drug-associated toxicity (laboratory blood testing at Day 1 between Day 3 to Day 7)

Clinical outcomes

- Change in ABSSSI lesion size
- Clinical resolution of symptoms
- Need for additional intravenous/oral antibiotic therapy

F Statistical Plan

F1 Sample Size Determination and Power

As this a feasibility study and none of the existing literature has defined the effect size of long-acting antibiotic therapy on healthcare utilization, healthcare cost, or patient satisfaction to the best of our knowledge, a sample size determination could not be performed. We are also limited by the number doses provided by Allergan to conduct this study.

F2 Interim Monitoring and Early Stopping

An interim analysis of adverse events will performed after every 10 patients. If we identify 5 or more adverse events possibly related to dalbavancin, we will suspend the study until we can have an Institutional Data and Safety Monitoring Board (consisting of 3 independent experts not involved in the study) perform a formal interim analysis to determine if there is a safety issue.

F3 Analysis Plan

All statistical analyses, apart from interim safety analyses described above, will occur at the end of study enrollment and after the final participant has completed their 28-day follow-up.

F4 Statistical Methods

Measures assessed in this study will include healthcare service utilization, healthcare-associated costs, patient satisfaction, patient safety, and clinical outcomes. Univariate comparisons among categorical variables will be conducted with Chi square test or Fisher's exact test, as approprirate. Comparisons among continuous variables will be performed using student's T-test, Mann Whitney U test, or other tests, as appropriate. A two-sided P value <0.05 will be considered statistically significant.

G Data Handling and Record Keeping

G1 Confidentiality and Security

Patients will be approached for participation in the privacy of their ED treatment room. Consent and treatment will also occur in this setting. Demographic, clinical, patient satisfaction, and healthcare cost and utilization data will be collected during the study through a combination of electronic medical record review, patient interview in a private setting, and informatics data retrieval to achieve the aims of the study and not invade the rights of participants to privacy of their personal information. Only the minimum necessary private patient information will be collected for the purposes of this study. Interventions will occur in a private clinical care setting.

All data will be stored in a secured environment. Initial data will be collected in the BJH ED and/or hospital on paper forms and entered into a secure REDCap database at a later time. A study number associated with participant will be listed on each data collection form. The paper record will be stored in a secure file cabinet in a locked office within the Division of Emergency Medicine ECRC, to which only the emergency medicine research coordinators will have access

to. Subsequent data collection using paper forms in the Infectious Diseases Clinic/ID-CRU will be stored in a secure file cabinet within the Division of Infectious Diseases, to which only the ID-CRU research staff will have access to, and will also be entered into the secure REDCap database at a later time.

Once data on paper forms have been abstracted to REDCap, study participant data will be de-identified, eliminating name and other personal identifiers, including medical record numbers. The study number will serve as the only means to link study participant data in REDCap back to the paper records. REDCap is a secure, password-protected electronic tool for capturing and storing research data, administered locally through the Washington University Institute of Clinical and Translational Sciences (ICTS).

G2 Training

All research staff associated with this study will have receive regularly formal training on HIPAA, ethical research conduct, and study-specific procedures and protocols.

H Study Administration

H1 Funding Source and Conflicts of Interest

This study is funded through by a Project Award through the Foundation for Barnes-Jewish Hospital. Study drug (dalbavancin) is provided without cost through an Investigator-Initiated Clinical Trial research grant through Allergan, the maker of dalbavancin. Allergan will have no influence in the design, conduct, analysis, or publication of the study and/or its findings as part of a fully-executed Agreement. We will provide quarterly and final updates to Allergan regarding the status of the study. Washington University will retain rights to the study data.

H2 Subject Stipends or Payments

Study participants will receive a $25 gift card at the time of study enrollment on Day 1 and at in-person follow-up between Day 3 and Day 7. Participant social security numbers will be collected solely for tax purposes and stored separate from study data.

I Publication Plan

We will submit a final report of the findings of this study to the Foundation for Barnes-Jewish Hospital and Allergan. It is our intent to publish study findings in a peer-reviewed medical journal.

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