Background

Staphylococcus aureus bacteremia is associated with serious complications and adverse patient outcomes, including infective endocarditis, in 30 to 40% of cases[1, 2]. Despite the usage of targeted therapy with anti-staphylococcal beta-lactam antibiotics, the mean duration of bacteremia remains between three and four days[3], with an accompanying 30-day mortality rates over 15% even in the absence of endocarditis[1, 4]. Persistent bacteremia on day three of appropriate antibiotic therapy is an independent risk factor for both endocarditis and mortality[4]. There is, therefore, a strong theoretical justification to reduce the duration of bacteremia in these patients. Recognizing this, the use of adjuvant gentamicin was formerly recommended to accelerate the clearance of bacteremia. Unfortunately, this practice was associated with renal toxicity, which outweighs any benefit in bacterial clearance and is no longer recommended[5]. Thus, a synergistic drug that would accelerate bacterial clearance without toxicity would represent a substantial finding of international importance.

Daptomycin is a cyclic lipopeptide antibiotic that is rapidly bactericidal in-vitro against most clinically relevant gram-positive organisms, including both methicillin-resistant and methicillin-sensitive S. aureus (MRSA and MSSA, respectively). Its unique mechanism of action involves the insertion of a lipophilic tail into the bacteria cell membrane in a calcium-dependent manner, which results in potassium ion efflux and subsequent membrane depolarization. The bacterium is then unable to perform DNA, RNA or protein synthesis, and undergoes cell death[6]. Daptomycin is approved for the treatment of complicated skin and soft tissue infections, as well as S. aureus bacteremia, but is not the standard of care due to drug costs.

We hypothesize that the use of a short course of daptomycin combined with the standard antibiotics used to treat MSSA (cefazolin or cloxacillin) may potentiate early bacterial clearance at a fraction of the cost required for a complete course. Daptomycin is used clinically in combination with beta-lactam antibiotics in the treatment of MRSA bacteremia in order to benefit from the "see-saw effect", whereby the beta-lactam helps maintain the organism's sensitivity to daptomycin. However, it has also been used in the treatment of refractory MSSA bacteremia with improved clinical outcomes[7]. *In-vitro* evidence suggests that the combination of an anti-staphylococcal beta-lactam and daptomycin results in improved bactericidal activity against MSSA[8, 9] and we hypothesize this property could be used *in-vivo* to improve patient outcomes. This phenomenon is explained, at least in part, by their synergistic activity, as beta-lactam exposure increases the net surface negative charge on the bacterial cell wall, which results in increased binding of the positively charged daptomycin-Ca^{2+} complex[7].

As of August 2016, on the major clinical trial registry websites there are no registered clinical trials looking to improve outcomes in MSSA bacteremia. This is unfortunate since MSSA bacteremia represents 75-80% of all *S. aureus* bacteremia at the McGill University Health Centre. From April 2010 to April 2015 there were 324 episodes of MSSA bacteremia[4]. As part of routine standard of care, patients are treated with an anti-staphylococcal beta-lactam antibiotic, have any catheters they may have removed to ensure adequate source control, and obtain an echocardiogram to rule out infective endocarditis. Despite these measures, approximately 45% of patients remained bacteremic at 3 days and our overall in-patient 30-day mortality rate was 16.3% (53 deaths)[4]. The objective of our study is thus to assess the efficacy and

safety of adding daptomycin to an anti-staphylococcal beta-lactam, as compared with standard therapy, for the treatment for MSSA bacteremia in adults. Based on power calculations, and accounting for death prior to outcome as well as patient refusal to participate, we believe that our study would require the enrollment of 102 patients to demonstrate our primary outcome, and will be completed within 18 months with an interim analysis at 12 months.

Methods

The DASH-RCT is a randomized, double-blind, placebo-controlled trial enrolling at three McGill University Health Center (MUHC) hospitals: the Montreal General Hospital, the Royal Victoria Hospital and the Montreal Neurological Institute. The research protocol was submitted to the MUHC Research and Ethics Board who granted approval of the study in November 2016. The trial is funded via internal funds received from the MUHC Association of Physicians.

Study Population

Eligible inpatients are aged 18 years or older with a documented MSSA bacteremia who are enrolled within a maximum of 72 hours of the culture being drawn and within 24 hours of the confirmation of *Staphylococcus aureus*. Patients are excluded if they are moribund due to other illnesses and are expected to expire within 5 days of potential recruitment, are clinically appropriate for admission to a critical care unit but are not going to receive critical care due to an advanced directive, or if they are unable to receive either ASBL monotherapy or a combination of ASBL and daptomycin exclusively. The latter precludes individuals with known type I hypersensitivity to the study drugs from

participating in the trial, as well as those with polymicrobial infections requiring additional antimicrobials. Patients for whom the use of open label daptomycin was felt to be indicated by the treating doctors were also excluded.

Our research team is notified of eligible patients via direct page coupled with an automatically generated fax when a new presumptive *S aureus* is identified in a blood culture. The microbiologic protocols followed to identify *S aureus* and determine methicillin-susceptibility are included in the appendix. After the organism is identified, patients are assessed for eligibility and approached for the study by trained personnel. If patients are unable to consent, the research team approaches their power of attorney for third-party consent.

Upon enrolment, each patient is assigned a unique numeric study identifier that will be used in the subsequent randomization and statistical analysis. Randomization for each unique identifier is performed in advance by permuted block with variable block size. The randomization table is held in confidence by the central research pharmacy which services all three sites. Investigators and study personnel outside of the research pharmacy do not have access to the randomization table.

Study Protocol

Enrolled patients are randomized to daptomycin and an ASBL or placebo and an ASBL. Daptomycin 6mg/kg/dose is administered intravenously once daily for five days in persons with normal renal function (See Tables 1 and 2 for details). This dose was chosen as it is the dose approved by Health Canada for the treatment of *S. aureus* bacteremia. In obese patients, the actual body weight is used as in keeping with the monograph. The study drug is dissolved in a 50mL bag of NaCl 0.9% or in an appropriate sized syringe if

there is a minibag shortage. The placebo is NaCl 0.9% which is provided in the same container and administered intravenously once daily for five days in persons with normal renal function; the dosing frequency is adjusted based on patient's renal function in the same manner as daptomycin (See Table 2).

The MUHC research pharmacy monitors the creatinine clearance of enrolled patients and contacts the research team to suggest dosing modifications as needed, regardless of drug allocation. The study drug is delivered to the patient's admitting unit in the form of a sealed container with the patient's name and unit number, as well as administration instructions.

The choice of ASBL, either cloxacillin or cefazolin, is at the treating team's discretion. Further management of the infection is also at the treating team's discretion. The study protocol does not prescribe the timing of removal of intravascular devices, performance of echocardiography, ancillary investigations aside from the bloodwork mentioned below, or consultation with an infectious diseases specialist. Statin therapy may be continued.

The study mandates that regular blood samples be obtained to document clearance of the infection and monitor for drug adverse effects. Two sets of aerobic and anaerobic blood cultures are obtained daily for five days or until microbiological clearance is documented. As per our routine hospital practice, the first blood culture set contains both an aerobic and an anaerobic bottle, whereas the second set contains only an aerobic bottle. Complete blood counts, creatine kinase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, and total and direct bilirubin are drawn on days 1 and 5. Electrolytes, blood urea nitrogen, and

creatinine are measured at a minimum on days 1, 3, and 5. In addition, each patient's first MSSA isolate undergoes full antimicrobial susceptibility testing, as well as MIC testing to daptomycin via the performance of a Daptomycin ETest (BioMérieux, France).

Treatment allocation is blinded to the patients, their clinicians, the investigators assessing the primary outcome, and those performing the statistical analysis. Unblinding can be requested by the treating physician in the event of a serious adverse event suspected to be due to the study drug. The research team is notified that the patient has been unblinded and excluded from receiving further study drug. However, the patient's allocation arm remains unknown to the investigators. Such patients are maintained in the intention to treat analysis.

The participants' data is collected and managed using REDCap electronic data capture tools hosted at the McGill University Health Centre [10]. Data are anonymized and de-identified to ensure patient confidentiality.

Outcomes

The primary outcome is to assess if the addition of five days of adjunctive daptomycin therapy to an ASBL, compared to ASBL monotherapy, will decrease the duration of MSSA bacteremia in hospitalized men and women 18 years of age or older. The total duration of bacteremia will be determined based on microbiology laboratory reports. The duration will be defined in days, where day 1 is the day on which the first positive blood culture was drawn and the final day is the last day which yielded a positive blood culture.

Secondary Outcomes:

1. All cause 30-day mortality will be obtained from hospital records and centralized provincial health care databases.

2. Relapsed bacteremia is defined as a blood culture specimen positive for MSSA obtained ≥ 48 hours and ≤ 90 days after obtaining a negative blood culture (negative after 5 days of incubation). Results will be obtained from the electronic microbiology laboratory records.

3. Clinically relevant embolic or metastatic MSSA disease will be diagnosed within 90 days of the first positive blood culture by the treating team and defined as the presence of: bone abscess or osteomyelitis on CT scan, MRI, or bone and gallium scan; renal emboli, or ilio-psoas, splenic and other occult abscesses on ultrasound, CT scan or MRI; septic brain emboli on CT head or MRI brain; septic emboli to the lung on chest x-ray or CT scan; infective endocarditis on echocardiography.

4. The patient safety outcome will be a combined endpoint of nephrotoxicity, as defined by the KDIGO guidelines[11], hepatotoxicity, as defined by an increase in liver enzymes three times the upper limit of normal, and rhabdomyolysis, as defined by an increase in creatine kinase three times the upper limit of normal, occurring within the first 7 days of therapy. A questionnaire administered on day 5 assesses for nausea, vomiting, headaches, and myalgias.

Statistical Analyses

Sensitivity analysis was performed to determine the sample size required to achieve 80% power. Assuming that the bacteremia time was normally, log-normally, or Poisson distributed, with a mean duration of bacteremia of 3 days, and a standard deviation of 2 days (3 for Poisson), a sample size of approximately 102 participants would

be required to detect a 1-day difference in duration of bacteremia at a significance level of 5%. If the mean duration of bacteremia is 2 days, we would have 70% power for our primary outcome assuming the bacteremia time was normally or log-normally distributed. Assumptions were adapted from a previously published study [12] and derived from our center's local epidemiology.

Participants will be analyzed according to their treatment allocation in an intention-to-treat analysis. A modified intention to treat analysis will exclude participants whose blood cultures were already negative at the time of their first study drug dose. Participants who have received at least 3 days of therapy according to their treatment allocation will also be analyzed in a per-protocol fashion as part of the secondary analyses.

Primary Outcome: the duration of MSSA bacteremia will be evaluated via time to event analysis using Kaplan Meier curves reporting the median time to clearance. Comparisons will be made using the Tarone-Ware log rank test with significant $\alpha<0.05$. Secondary Outcomes:
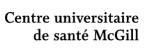
1. The proportion who have cleared their MSSA bacteremia at days 3, 5, and 7.

2. Relapsed bacteremia will be a binary outcome; proportions will be reported, compared with Fisher's Exact Test.

3. Metastatic MSSA disease will be a binary outcome; proportions will be reported, compared with Fisher's Exact Test.

4. The patient safety outcome will be binary; proportions will be reported, compared with Fisher's Exact Test, then we will adjust for confounders using exact logistic regression.
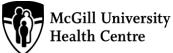
5. Analysis for effect modification of the primary outcome using cox regression models. We will analyze for patient comorbidities, including immunosuppressive conditions, the presence of endocarditis, source control difficulties, metastatic MSSA infection, and an infectious diseases consultation.

6. Accounting for confounders: imbalances in potential confounders between study arms will be evaluated for their influence on the relationship between the intervention and the time to clearance of bacteremia using cox regression models. Exact logistic regression will be used to adjust for confounders of the secondary outcomes (#1 through #4).

7. Per protocol analysis of the time to clearance of bacteremia between the study groups; time to event analysis using Kaplan Meier curves, comparisons using the Tarone-Ware log rank test.

An interim analysis is planned upon enrolment of 50 patients who remain bacteremic at the time of enrollment. This analysis will be reviewed by an independent Safety Monitoring Board comprised of 2 physicians and 1 statistician who are not appointed to the division of Infectious Diseases and are not involved in the study. They have the authority to stop the study if there is significant evidence of benefit or harm (primary outcome, primary safety outcome) based on the an O'Brien-Fleming alpha-spending approach [13].

References

1. Chang, F.Y., et al., *A prospective multicenter study of Staphylococcus aureus bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance.* Medicine (Baltimore), 2003. **82**(5): p. 322-32.
2. Fowler, V.G., Jr., et al., *Clinical identifiers of complicated Staphylococcus aureus bacteremia.* Arch Intern Med, 2003. **163**(17): p. 2066-72.
3. Fowler, V.G., Jr., et al., *Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus.* N Engl J Med, 2006. **355**(7): p. 653-65.
4. Cheng, M.P., et al., *Back to the Future: Penicillin-Susceptible Staphylococcus aureus.* Am J Med, 2016.
5. Leis, J., et al., *Choosing Wisely Canada - top five list in infectious diseases: An official position statement of the Association of Medical Microbiology and Infectious Disease (AMMI) Canada.* Journal of the Association of Medical Microbiology and Infectious Disease Canada, 2016. **1**(1): p. 8 - 12.
6. Silverman, J.A., N.G. Perlmutter, and H.M. Shapiro, *Correlation of daptomycin bactericidal activity and membrane depolarization in Staphylococcus aureus.* Antimicrob Agents Chemother, 2003. **47**(8): p. 2538-44.
7. Dhand, A. and G. Sakoulas, *Daptomycin in combination with other antibiotics for the treatment of complicated methicillin-resistant Staphylococcus aureus bacteremia.* Clin Ther, 2014. **36**(10): p. 1303-16.
8. El Haj, C., et al., *Comparative efficacies of cloxacillin-daptomycin and the standard cloxacillin-rifampin therapies against an experimental foreign-body infection by methicillin-susceptible Staphylococcus aureus.* Antimicrob Agents Chemother, 2014. **58**(9): p. 5576-80.
9. Snydman, D.R., L.A. McDermott, and N.V. Jacobus, *Evaluation of in vitro interaction of daptomycin with gentamicin or beta-lactam antibiotics against Staphylococcus aureus and Enterococci by FIC index and timed-kill curves.* J Chemother, 2005. **17**(6): p. 614-21.
10. Paul A. Harris, R.T., Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde, *Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform., 2009 Apr. **42**(2): p. 377-381.
11. Ardalan, M.R., et al., *Aspergillosis after renal transplantation.* Saudi J Kidney Dis Transpl, 2005. **16**(3): p. 330-3.
12. Davis, J.S., et al., *Combination of Vancomycin and β-Lactam Therapy for Methicillin-Resistant Staphylococcus aureus Bacteremia: A Pilot Multicenter Randomized Controlled Trial.* Clinical Infectious Diseases, 2016. **62**(2): p. 173-180.
13. DeMets, D.L. and K.K. Lan, *Interim analysis: the alpha spending function approach.* Stat Med, 1994. **13**(13-14): p. 1341-52; discussion 1353-6.

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PRESCRIPTION DE RECHERCHE CLINIQUE
CLINICAL RESEARCH PRESCRIPTION

ALLERGIES _____   **Poids** / Weight (kg) _____

Initiales du médecin pour chaque ordonnance Physician's initials for each order	ORDONNANCE DU MÉDECIN / PHYSICIAN'S ORDERS	Initiales de l'infirmier(ère) notées Nurse's initials noted
	Étude de recherche clinique / Clinical study	
	DASH / 2017-2666 Daptomycin as Adjunctive Therapy for Staphylococcus Aureus Bacteremia Dr. Todd Lee Initiales du patient/Patient initials: _____ - _____ - _____ Numéro de patient/ patient number :	
	Daptomycin 6 mg/kg or placebo in 50 ml NS IV over 30 minutes Dose = _____ mg (see Dose/Weight chart) Based on _____ kg Dosing interval = _____ H (see Frequency/CrCl chart)	

Daptomycin dose:	
Weight	Daptomycin Dose
38 - 45 kg	250 mg
46 - 54 kg	300 mg
55 - 62 kg	350 mg
63 - 70 kg	400 mg
71 - 79 kg	450 mg
80 – 87 kg	500 mg
88 – 95 kg	550 mg
96 – 104 kg	600 mg
105 – 112 kg	650 mg
113 – 120 kg	700 mg
121 – 129 kg	750 mg
130 – 137 kg	800 mg
138 – 145 kg	850 mg
More than 145 kg	900 mg

Daptomycin frequency:	
CrCl (ml/min)	Daptomycin Frequency
30 or more	Q24H x 5 days
< 30	Q48H x 3 doses
If CRRT	Q24H x 5 days
If CAPD	Q48H x 3 doses
If IHD	qIHD x 3 doses**

** For IHD, check appropriate option:
☐ Give each dose after hemodialysis sessions.
OR
☐ Give one dose now, and next two doses after the following hemodialysis sessions

	☐ Stop DASH if patient is discharged home or transferred to a hospital other than the Royal Victoria Hospital, Montreal General Hospital, and Montreal Neurological Hospital	
	Standard of care management for all Staphylococcus aureus bacteremias ☐ Continue current antibiotics as per the treating team	
	****Please fax to - Clinical Research Pharmacy 8am to 4pm GLEN 514-843-2867 / MGH 514-934-8497/ MNH 514-843-1474 / AFTER hours and w-e phone GLEN 36550 / MGH 42941 ****	

	Nom en lettres moulées Name in print	Signature	N° Permis License No.	Heure/Time 00:00	Date AAYY/MM/JD
Médecin Physician					

	Nom en lettres moulées et/ou numéro de permis Name in print and/or license number	Initiales Initials	Heure/Time 00:00	Date AAYY/MM/JD
Infirmier(ère) Nurse				
Pharmacien(ne) Pharmacist				