COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project
Sub-Intern Name: Monika Laszkowska **Block:** June **Date:** 6/28/2013

Case SIGNOUT

The patient is a 44yo male with a history of type 2 diabetes and hypertension who presented with right lower extremity swelling and erythema for 5 days. He initially noted cramping in his right leg, which the following day progressed to swelling, pain, and erythema from the knee to the ankle along the anterior surface of the leg. He took penicillin twice daily for the next 3 days (dose & source unknown), but his symptoms did not improve so he presented to the ED. He denies any trauma to the leg & has no history of skin infections or diabetic foot complications. He denies fevers, chills, SOB, chest pain, N/V, abdominal pain, changes in BMs or dysuria. In the ED, vital signs were WNL. Lower extremity ultrasound was consistent with cellulitis and a possible abscess. Blood cultures were positive for MRSA. He was initially treated with Cefazolin, Vancomycin, and Piperacillin/Tazobactam, which was narrowed to Vancomycin alone when cultures grew Staphylococcus aureus, later found to be methicillin-resistant S. aureus (MRSA). Sensitivities for Vancomycin were 2 S and for Daptomycin <0.5 S. ECHO showed no evidence of endocarditis.

Clinical Question: Is Daptomycin an effective alternative to Vancomycin for treating S. aureus bacteremia?

Background:

S. aureus bacteremia: Leading cause of community-acquired & hospital-acquired bacteremia.

- **Complications**: almost any body site can become secondarily infected
  - Infective Endocarditis – 10-15% cases; increase in severe sepsis, multi-organ failure, & higher mortality
  - Prosthetic Device Infection – risk with PMMs, ICDs, orthopedic devices
  - Waterhouse-Friderichsen Syndrome – petechial rash, coagulopathy, cardiovascular collapse, and adrenal hemorrhage. Low risk but devastating. If see this presentation cover for MRSA.
  - Metastatic Seeding – vertebral osteomyelitis, septic arthritis, splenic abscess, thrombophlebitis, CNS infection, pulmonary infection, soft tissue infection, bacteriuria

Risk Factors for MRSA:

◆ Diabetes	◆ Recent/long hospitalization	◆ Recent antibiotic therapy	◆ IV drug use
◆ Incarceration	◆ Military service	◆ Long-term care facility	◆ HIV infection
◆ MSM	◆ Sharing sports equipment	◆ Sharing needles/razors	◆ HD

Treatment Strategies: No randomized controlled trials for empiric regimens – based on likelihood of MRSA Mortality is higher in MRSA (34%) than MSSA (20%).

- **Standard Treatment** = **Vancomycin** (glycopeptide inhibits cell wall synthesis; 30 mg/kg/24h in 2 doses)
  - If confirm MSSA, switch to a beta-lactam (IV nafcillin, oxacillin, flucloxacillin outside US) or cefazolin. Beta lactams are superior to and safer than Vancomycin.
- **Vancomycin Resistance**: Susceptible: MIC ≤2 mcg/mL Intermediate: MIC 4 to 8 mcg/mL Resistant: MIC ≥16 mcg/mL
  - A 2012 meta-analysis observed increased mortality with MRSA bacteremia when vancomycin MIC was ≥2 mcg/mL (OR 1.72, 95% CI 1.34-2.21) but not in cases with MIC ≤1.5 mcg/mL
- **Daptomycin** = cyclic lipopeptide bactericidal antibiotic that causes depolarization of the bacterial cell membrane
  - A 2012 retrospective case control study of 177 patients with MRSA bacteremia, high vancomycin MIC (>1 mcg/mL) had higher mortality than treatment with daptomycin (20% versus 9%)

Search Strategy

- Database: Pubmed Search Terms: (staphylococcus aureus[MeSH Terms]) AND bacteremia[MeSH Terms]) AND "randomized controlled trial"[Publication Type]) AND "english"[Language] → 28 results
- Chosen Publication: Fowler VG Jr, Boucher HW, Corey GR, Abrutyn E, Karchmer AW, Rupp ME, Levine DP, Chambers HF, Tally FP, Vigliani GA, Cabell CH, Link AS, DeMeyer I, Filler SG, Zervos M, Cook P, Parsonnet J, Bernstein JM, Price CS, Forrest GN, Fätkenheuer G, Gareca M, Rehm SJ, Brodt HR, Tice A, Cosgrove SE; S. aureus Endocarditis and Bacteremia Study Group. Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus. N Engl J Med. 2006 Aug 17;355(7):653-65.

Senior Medicine Rotation: Based Medicine Project (Cont)

Group	Criteria or definition	n
Population screened	Patients from 44 sites in four countries	246
Inclusion criteria	>18yo and had 1+ cultures positive for S.aureus within 2 days before initiating study medications	235
Exclusion criteria	CrCl>30mL/min, known osteomyelitis, polymicrobial bacteremia, or pneumonia	11
Treatment group	Daptomycin 6mg/kg IV daily (and gentamycin 1mg/kg IV Q8H for first 4 days in pts with L-sided endocarditis)	120
Standard therapy group	Standard therapy with either Vancomycin 1g Q12H (dose-adjusted) OR antistaphylococca penicillin (nafcillin, oxacillin, or flucloxacillin) 2g Q4H based on sensitivity AND gentamycin 1mg/kg IV Q8H for first 4 days	115

Primary endpoint: Overall success rate in each of the two treatment groups in the modified intention-to-treat population at a visit 42 days after the end of therapy.

Secondary endpoints: Components of treatment failure: clinical failure, microbiologic failure, death, failure to obtain blood culture, receipt of potentially effective non-study antibiotics, or premature discontinuation of the study meds because of clinical/microbiologic failure or adverse event.

- Are the Results of the Trial Valid?
  - Randomized? YES. 246 patients were randomly assigned to one of two study arms using a block randomization schedule (goal of 1:1 ratio of patients stratified according to site).
  - All patients accounted for at end? YES. 246 patients were randomized. 11 patients were excluded from the modified intention-to-treat population. 10 patients did not receive the study drug (6 in daptomycin group, 4 in standard treatment group). 1 patient was treated with standard therapy and enrolled before the amendment to allow patients with a high likelihood of left-sided endocarditis.
  - Intention to treat? YES. Intention to treat population included all randomized patients. Modified intention-to-treat population included randomized patients who received at least one dose of study medication except 1 pt with a high likelihood of left-sided endocarditis enrolled before a protocol amendment allowing inclusion.
  - Blinding? NO. Investigators treating the patients were not blinded; however, a committee of 5 infectious disease experts who were unaware of patients' treatment assignments reviewed data from each patient to establish the diagnosis and outcome.
  - Groups similar at start of trial? YES. There were no statistically significant differences in age, sex, ethnic group, BMI, CrCl, risk factors for S. aureus infection (DM, SIRS, IV drug use, preexisting valve disease, surgery in last 30 days, extravascular foreign material, or septic pulmonary emboli), or rates of MRSA infection. Final diagnoses were similarly distributed in the treatment groups. The only statistically significant difference in the two groups was rate of HIV infection (6.7% in daptomycin group vs. 0.9% in standard therapy group, P=0.04).
  - Equal treatment of groups? YES. Investigators evaluated all patients at baseline, at end of therapy, and 42 days after end of therapy. Duration of therapy was determined by the investigator on the basis of the working diagnosis. Blood cultures were done daily until were negative, and at end of therapy and at 42 days. All patients got TEE within 5 days of starting meds (all were reviewed by independent expert). All patients who received at least one dose were included in safety analyses.
  - Did randomization work? YES.

- Are the Results of the Trial important?
  - Size of treatment effect? There is no significant difference between the two groups in primary or secondary outcomes, so dapromycin is not inferior to standard therapy. While there were some differences in secondary endpoints, these were not statistically significant. The window for non-inferiority was rather large (lower bound of confidence interval at 20%). Furthermore, an inherent bias of a non-inferiority trail is that there can be bias by assigning similar ratings to all patients.
  - Precision of the estimate of the effect? The study has a relatively large sample size with high exposure, which suggests the estimate is likely fairly precise.

Type of Study: Randomized non-inferiority trail (lower limit of 95%CI is -20%)

Endpoint	Result		Significance (Absolute Difference in Success Rates) % (95% CI)
	Daptomycin	Standard Tx	
Primary Overall Success	53/120 (44.2%)	48/115 (41.7%)	2.4 (-10.2 to 15.1)
- Success in MSSA	33/74 (44.6%)	34/70 (48.6%)	-4.0 (-20.3 to 12.3)
- **Success in MRSA (P=0.28)**	20/45 (44.4%)	14/44 (31.8%)	**12.6 (-7.4 to 32.6)**
Success in Predefined Strata			
1. Uncomplicated bacteremia			
- MSSA	12/21 (57.1%)	11/17 (64.7%)	-7.6 (-38.6 to 23.5)
- **MRSA**	6/10 (60%)	5/11 (45.5%)	**1.1 (-15.6 to 17.8)**
2. Complicated bacteremia + R-sided endocarditis			
- MSSA	20/49 (40.8%)	21/48 (43.8%)	-2.9 (-22.6 to 16.7)
- MRSA	14/30 (46.7%)	9/29 (31%)	15.6 (-8.9 to 40.2)
3. Definite + possible endocarditis			
- MSSA	26/54 (48.1%)	26/53 (49.1%)	-0.9 (-19.8 to 18.0)
- MRSA	15/36 (41.7%)	11/38 (28.9%)	12.7 (-8.9 to 34.3)
Secondary Endpoints:			**P Value**
Overall Failure	55.8%	58.3%	
Microbiologic failure, clinical failure, or both	19.2%	13%	0.22
Microbiologic failure	15.8%	9.6%	0.17
Clinical failure without microbiologic failure	3.3%	3.5%	1.00
Adverse event	6.7%	14.8%	**0.06**
Receipt of non-study antibiotics	16.7%	13.9%	0.59
Death	10.8%	11.3%	1.00
No blood obtained for culture	7.5%	10.4%	0.50
Patient could not be evaluated	7.5%	12.2%	0.27
Morbidity	**Result**		**Significance (P Value)**
	Daptomycin	**Standard**	
Any drug-related adverse event	42 (35%)	49 (42.2%)	0.29
Any serious event	62 (51.7%)	52 (44.8%)	0.3
Any drug-related serious event	3 (2.5%)	6 (5.2%)	0.33
Most common adverse events:			
- Anemia	15 (12.5%)	18 (15.5%)	0.58
- Diarrhea	14 (11.7%)	21 (18.1%)	0.20
- Vomiting	14 (11.7%)	15 (12.9%)	0.84
- Constipation	13 (10.8%)	14 (12.1%)	0.84
- **Nausea**	**12 (10%)**	**23 (19.8%)**	**0.04**
- Hypokalemia	11 (9.2%)	15 (12.9%)	0.41
- **Renal Impairment**	**8 (6.7%)**	**21 (18.1%)**	**0.009**
- Headache	8 (6.7%)	12 (10.3%)	0.36
- Peripheral Edema	8 (6.7%)	16 (13.8%)	0.09
- **Arthralgia**	**4 (3.3%)**	**13 (11.2%)**	**0.02**
- **CK elevation**	**8 (6.7%)**	**1 (0.9%)**	**0.04**

Can I apply these results to my patient?

- Comparison of my patient to trial patients: My patient would have met the inclusion criteria for the study, and the exclusion criteria would not apply to him. While he fits most of the characteristics of the patients in the study (age, sex, BMI, renal function), he is Hispanic and this group is not well represented in the sample (n=13/236). Furthermore, there were 99 patients with MRSA bacteremia, but only 21 of these had uncomplicated bacteremia like my patient does.
- All clinically important outcomes considered: MOST LIKELY. The primary factors to consider include efficacy as well as potential harm. This study looked at all possible reasons for treatment failure ranging from clinical/biological to logistical. Furthermore, an extensive list of side effects was considered. Financial factors were not incorporated into the analysis, but would be interesting to assess.
- Likely benefits outweigh potential harms and cost: UNCLEAR. The clinical decision to be made in this patient is whether or not to transition from vancomycin to daptomycin.

  Benefits to transitioning to daptomycin:
  - Based on the results of this randomized trial, daptomycin is not inferior to standard therapy in success rates or overall side effect profile and may be a valid treatment alternative for this patient.
  - This data may suggest that daptomycin is more effective than standard therapy in MRSA bacteremia; however, that difference is not statistically significant and this trail was not designed to validate this premise.
  - The patient's susceptibility to vancomycin is a MIC of 2 S. There are no randomized controlled clinical trails that show that this level of resistance is significant enough to merit a change in treatment; however, there is some

convincing evidence from retrospective and cohort studies to suggest a potentially high rate of treatment failure of vancomycin when MIC is >/=2.

- The strongest data for daptomycin from other studies are in the setting of complicated skin infections and bacteremia, which fits this patient's presentation.
- Given that this patient is a diabetic, it may be favorable to spare him from potential renal toxicity of vancomycin.

Costs/harms of transitioning to daptomycin:

- While this trail demonstrated non-inferiority of daptomycin as compared to vancomycin, there is no evidence that daptomycin will actually be more effective in treating this patient's infection.
- Given that vancomycin is the standard of therapy for MRSA bacteremia and this has been the case for many years, clinicians have far more experience in using vancomycin for treatment of MRSA bacteremia.
- Daptomycin is associated with significantly higher elevation in CK than standard therapy, which would require monitoring the patient while he is on this treatment.

References:

- Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis. 2004;38(12):1673.
- van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in Staphylococcus aureus infections: a systematic review and meta-analysis. Clin Infect Dis. 2012 Mar;54(6):755-71.
- Moore CL, Osaki-Kiyan P, Haque NZ, Perri MB, Donabedian S, Zervos MJ. Daptomycin versus vancomycin for bloodstream infections due to methicillin-resistant Staphylococcus aureus with a high vancomycin minimum inhibitory concentration: a case-control study. Clin Infect Dis. 2012;54(1):51.
- Murray KP, Zhao JJ, Davis SL, Kullar R, Kaye KS, Lephart P, Rybak MJ. Early use of daptomycin versus vancomycin for methicillin-resistant Staphylococcus aureus bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. Clin Infect Dis. 2013 Jun;56(11):1562-9. doi: 10.1093/cid/cit112. Epub 2013 Feb 28.
- Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, J Rybak M, Talan DA, Chambers HF. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis. 2011 Feb 1;52(3):285-92.