

A Review of Daptomycin vs. Vancomycin for Susceptible Infections: Is One Superior for Outpatient Parenteral Antibiotic Treatment (OPAT)?

Daniel Decker
PharmD, MBA, BCACP
Option Care Health

dr.daniel.decker@
gmail.com

ABSTRACT

Background

Outpatient Parenteral Antibiotic Treatment (OPAT) is becoming a more frequent modality of completing a patient's antimicrobial treatment to save on hospitalization costs and decrease the risk of nosocomial infections. The use of vancomycin, a widely used medication in OPAT, may mitigate some of those savings due to dosing and lab monitoring challenges, adverse drug reactions (ADRs), clinical failure rate, and re-hospitalization risk associated with the drug. The objective of this review is to examine if daptomycin is a safer, more effective, and cost-saving medication to the health care continuum when used in the OPAT setting.

Methods

A literature review was conducted to evaluate the comparative rate of effectiveness, treatment failure due to adverse event (ADE), patient satisfaction, antimicrobial stewardship concerns, and potential cost comparisons of daptomycin and vancomycin.

Results

Daptomycin was shown to have a higher clinical success rate when used in OPAT vs. inpatient (94.6% vs. 86.3%) and a higher success rate vs. standard therapy for *S. aureus* when used in OPAT (90% vs. 83%). Compared to vancomycin, daptomycin decreased rate of clinical failure (OR 0.58), had a lower rate of discontinuation due to ADE (OR 0.15), less severe ADE, was associated with higher patient satisfaction, and is considered the superior treatment at a willingness to pay threshold above \$15,000 for severe infections.

Conclusion

According to the literature review, daptomycin may be superior to vancomycin for severe infections in the OPAT setting.

Key Words: *daptomycin, vancomycin, OPAT, AKI, WTP*

Introduction

The long duration of treatment necessary for severe infections and the high cost of inpatient hospital care have led insurance companies and health care providers to turn to outpatient parenteral antibiotic treatment (OPAT) to complete a patient's treatment course once they are stable for discharge. The global home infusion market, a large purveyor of OPAT, has an expected compound annual growth rate of 11% from 2021 through 2027, which has accelerated in recent years due to COVID shifting more care to the patient's home.¹ While OPAT adds significant cost savings, it is not without additional risks and challenges. When considering OPAT, all the risks of clinical failures are amplified as the patient is no longer in a hospital bed available for labs and doses at the provider's request. Therefore, patient compliance with dosing, labs, hydration, and other factors is paramount in determining clinical success or failure.

Vancomycin has been used for several decades in the hospital setting for parenteral treatment of severe gram-positive bacterial infections. While vancomycin's efficacy is still robust after many years, concerns about its toxicity, such as acute kidney injury (AKI), is often at the forefront of providers' minds. The risk of AKI increases with higher doses needed to obtain the necessary 15-20mg/L trough levels and durations longer than 2 weeks, which are frequently required to treat severe susceptible infections.²⁻⁴ *Cano et al.*, found that patients on vancomycin with a goal trough of 15-20mg/L for longer than 7 days increased their risk of AKI by 12% for every additional day they were treated.^{3,5} *Hidayat et al.* showed 30% of patients on high-dose vancomycin treated for greater than 2 weeks suffered nephrotoxicity.^{5,6} To minimize adverse effects and verify the drug concentration is appropriate for treatment, vancomycin has strict lab monitoring requirements depending on the method of dose monitoring, which places an additional cost, time, and convenience burden over other traditional antimicrobials. Despite AKI being a likely morbidity for many of these patients, vancomycin is one of the most common drugs infused in the home setting.^{7,8}

With a heightened focus on the cost of care, clinicians are faced with analyzing if a drug will be effective from both a clinical and a cost-effectiveness standpoint. To understand some of the possible cost impacts of vancomycin unrelated to the direct drug cost, *Jeffres*

analyzed the impact toxicities, lab costs, and provider time have on the health care continuum.⁹ From a toxicity standpoint, *Jeffres* noted that nephrotoxicity occurs on average within 4 to 17 days after the start of therapy and is highly correlated with higher doses, length of therapy >7 days, and patients receiving additional nephrotoxic drugs.^{9,10} These factors can significantly increase the hospital length of stay (LOS) by 3.5 to 15 days (depending on the study and hospital ward) which also increases total medical cost (17.7% - 23.9%).^{4,9} Monitoring vancomycin levels and dosing vancomycin can also be costly, as patients can require lab draws up to biweekly depending on their acuity and risk factors which have associated lab-related costs and nursing time. Additionally, if providers wish to follow the 2019 Infectious Diseases Society of America (IDSA) guidelines and use the recommended area-under-the-curve (AUC) dosing instead of trough-based dosing, their choices are additional lab draws needed for the calculation or the use of software with Bayesian modeling, which can cost an organization tens of thousands of dollars per year.^{9,11,12} *Jeffres* also found that the mean cost to prevent 1 episode of vancomycin-related nephrotoxicity is \$25,167, and the cost to treat said nephrotoxicity is \$11,234.⁹ When totaled, this comes to a willingness to pay (WTP) to avoid 1 episode of vancomycin-related nephrotoxicity of approximately \$40,000, which was corroborated in a cost-effectiveness analysis performed in 2021 by *Vu et al.*¹³ Most of these costs could be eliminated or reduced by using alternative antimicrobials.

Since administering vancomycin safely poses many challenges, clinicians have looked for alternatives that may simplify the infusion process while adequately treating the patient's condition and preventing readmission. Daptomycin, a lipopeptide antibiotic released under the trade name Cubicin® in 2003, is used to treat infections resistant to vancomycin but also shares a similar efficacy profile for gram-positive bacterial infections such as methicillin-resistant *Staphylococcus aureus* (MRSA).^{8,14} With its once-daily dosing, lower rate of serious adverse drugs events (ADEs), less stringent lab monitoring requirements, and dosing that is less likely to require titration, daptomycin is often viewed as a safer, less complicated alternative which may decrease overall costs to the health care continuum while preserving clinical outcomes.^{2,14,15} However, the higher drug cost of daptomycin, which can be a multiple of 4 to 12x

the cost of vancomycin, and inpatient antimicrobial stewardship ideology have been barriers to more frequent use.¹⁶

The objective of this review is to analyze the available literature comparing clinical outcomes due to treatment failure, failure due to ADEs, ease of use, and patient satisfaction as possible contributors for clinical failure. Additionally, this study seeks to assess the total costs associated with treatment for both medications reflecting the cost burden clinical failures have on the health care continuum. Finally, this review will discuss which antimicrobial has a stronger case for use in OPAT regarding the challenges associated with therapy in this setting.

Methods

A literature search was conducted using the University of Florida online library Primo search function and Google Scholar from 2007 through 2022, emphasizing literature published since 2012 with full text copies available. The following search terms were used: “vancomycin,” “daptomycin,” “opat,” “copat,” “mrsa,” and “cost” in a variety of and/or combinations. A bibliography search was conducted to obtain additional resources.

Results

Clinical Efficacy and Effectiveness

Many studies have tried to capture various facets of clinical effectiveness by analyzing clinical failure rates and reasons for clinical failure. A significant contributor to clinical failure is the early discontinuation of an antimicrobial due to an ADE. *Maraolo et al.* noted in their meta-analysis comparing daptomycin and vancomycin for the treatment of MRSA bloodstream infections with or without endocarditis that daptomycin had an odds ratio of 0.15 compared to vancomycin for discontinuation due to adverse effects.¹⁷ Additionally, no significant difference in mortality but a significantly lower risk of clinical failure (OR 0.58) was found for daptomycin.¹⁷

Daptomycin has also been shown to have a higher success rate in the OPAT versus institutional setting. Results from the Cubicin Outcomes Registry and Experience (CORE), which was a post-marketing analysis, demonstrated that the clinical success rate of daptomycin in OPAT exceeded its inpatient success rate of 94.6% to 86.3% ($p < 0.001$), respectively.¹⁸ *Rehm et al.* showed a clinical success rate of 90% vs. 83% for daptomycin compared to standard therapy

for *S. aureus* infections in OPAT.¹⁹ Daptomycin also demonstrated a lower infection relapse rate (3.9% vs. 15.5%, $p = 0.007$), a lower mortality rate 6 weeks after completion of therapy (3.9% vs. 18.6%, $p = 0.001$), and a much higher clinical success rate over inpatient antibiotic therapy (86.4% vs. 55.7%, $p < 0.001$) vs. standard of care.¹⁹ *Seaton et al.* corroborated these results, analyzing the European Registry for daptomycin usage in OPAT and showing an 89% clinical success rate over a wide range of susceptible infections.²⁰ Noteworthy for these studies was that OPAT patients tended to be younger and have fewer comorbidities when compared with those who finished their therapy in the hospital; however, these factors are unlikely to favor one therapy over another for OPAT but more likely to impact the decision to service the patient institutionally or via OPAT.¹⁸⁻²⁰ This insinuates that while it is considered at least as effective as vancomycin in the hospital setting, data suggests better efficacy when used in the less controlled environment of OPAT.

While treatment failure from an ADE is a concern from an inpatient perspective, it is an even greater concern in OPAT due to the increased possibility of treatment failure. *Shrestha et al.* analyzed a single center cohort receiving vancomycin and daptomycin over a 3-year period to compare adverse events, health care interventions, and health care utilization during their OPAT course, which was standardized to a rate per 1,000 OPAT days.⁸ It was determined that vancomycin had more than double the ADE rate ($p = 0.02$) and 4.8x the rate of antimicrobial interventions ($p < 0.001$) than daptomycin patients.⁸ *Schrank et al.* conducted a retrospective analysis among OPAT patients receiving vancomycin vs. daptomycin over a 3-year period analyzing change or discontinuation of antimicrobial due to an ADE occurring greater than 7 days prior to the end of therapy.¹⁵ After adjusting for multiple differences in patient population characteristics, the ADE rate leading to a change or early discontinuation of treatment was 19.0% vs. 7.6% ($p < 0.01$) for vancomycin and daptomycin respectively, which typically would happen earlier in the treatment course ($p < 0.01$) for vancomycin.¹⁵ Additionally, the vancomycin group was 3.7x more likely to have an ADE (OR = 3.71, $p < 0.01$) related to discontinuation of treatment than the daptomycin group.¹⁵ The severity of ADE was notable, with the vancomycin group's most prevalent ADE being renal involvement (32% of ADE, 6% of patients overall), hypersensitivity

reactions (22% of ADE, 4.2% of patients overall), and cytopenias (10% of ADE, 1.9% of patients overall), vs. asymptomatic CK elevation of a 10-fold increase above the upper normal limit (50% of ADE, 4% of patients overall) and rhabdomyolysis (38% of ADE, 3% of patients overall) for daptomycin.^{14,15} A confounder mentioned by the authors was a significant difference in the location of OPAT, with significantly more patients on vancomycin receiving treatment in a long-term acute or skilled nursing facility ($p < 0.01$).¹⁵ This population tended to have a higher burden of comorbidities which could contribute to a higher likelihood of ADE.¹⁵ However, this population had a lower risk of medication changes due to ADE which may be explained by quicker access to hydration and the availability of hypersensitivity reaction abortive medications, which may have prevented a medication change.¹⁵ While these results are higher than the discontinuation rate of daptomycin documented in the European Registry, showing 3.1% of patients discontinued treatment related to ADE, daptomycin still demonstrates advantages over vancomycin regarding ADE.²⁰

Patient Adherence and Contributing Factors to Treatment Success

Often overlooked facets of OPAT outcomes include patient adherence, satisfaction, and perceived burden on their daily life. *Neiman et al.* noted that half of prescribed medications are taken incorrectly with regards to timing, dosage, frequency, and duration, which has a significant impact on treatment success, hospital readmission, and cost of care.²¹ *Wu et al.* assessed some of these issues by conducting a short telephone survey with patients treated with daptomycin or vancomycin to assess the impact on a patient's daily routine, ADE, hospital readmission, and time off work, which was collated into a daily impact score.²² Patients received daptomycin every 24 hours, while vancomycin patients received doses ranging from every 8 hours to every 48 hours, with every 12 hours being the most prevalent.²² The results demonstrated a higher daily impact score for vancomycin patients and a higher overall subjective satisfaction with daptomycin over vancomycin therapy (100% vs. 67% rated satisfaction of 8/10 or better on a 0-10 rating scale, respectively) which may be attributed to vancomycin infusions having a more varied frequency schedule along with 1-2 hours per infusion vs. once-daily dosing of daptomycin which is infused in 30 minutes or less.^{2,14,21} Patient perceived daily impact of therapy and patient

adherence to therapy could contribute to a much higher completion rate of daptomycin OPAT therapy vs. standard of care noted by *Rehm et al.* showing a 90.3% vs. 45.4% ($p < 0.001$) respectively.¹⁹

The antimicrobial stewardship community has taken note of this nuance as it demonstrates the difference between antimicrobial stewardship in the inpatient realm vs. OPAT. The usual doctrine of the antimicrobial stewardship community is the desire to preserve the efficacy of newer, novel, or broader-spectrum treatments by using older, more established treatments first, reserving the newer treatments for use only when initial treatment has failed.¹⁶ This would favor vancomycin over daptomycin, which is evident in many hospitals' treatment protocols. However, *Mahoney et al.* addressed this stating that while a narrower-spectrum agent over a broader one may be a priority in the inpatient setting, the OPAT setting focuses on ease of administration and convenience which are factors that can affect patient adherence, completion of therapy, and antimicrobial resistance in the community setting.¹⁶

Total Health Care Costs

Several authors endeavored to quantify the economic benefit of using various MRSA-focused antimicrobials to determine whether there is an advantage of using one over another. *Patel et al.* attempted to create an economic model which included a cost-minimization and cost-effectiveness analysis of daptomycin, vancomycin, and linezolid for MRSA acute bacterial skin and skin structure infections (ABSSSI) for which institutional and OPAT direct costs were included.²³ While they concluded vancomycin was significantly more cost-effective than daptomycin (18.5% lower cost of treatment), some limitations significantly favored vancomycin.²³ In the base-case and the scenario 1 sensitivity analysis, they assumed the same LOS regardless of the drug, which can be refuted by multiple studies that show daptomycin has a shorter time to clinical success.²³ Additionally, the scenario 3 sensitivity analysis used efficacy rate instead of clinical success rate (effectiveness), which would include treatment failures from ADE.²³ Since they included OPAT in this analysis, the clinical success rate would have been a better surrogate for real-world scenarios, as ADE have a large impact on patients completing a course of antimicrobials. Finally, the authors analyzed vancomycin ADE cost impact during the first 3 days of treatment (empiric phase) which increased the

favorability of vancomycin since studies have shown the longer a patient is on vancomycin, the more likely they are to have an ADE.^{6,23}

While the data is mixed on which is superior for ABSSSI due to the shorter duration of treatment and lower drug level targets needed, data analyzing more severe infections requiring a longer duration of treatment paints a different picture. *Vu et al.* completed an exploratory cost-effectiveness analysis that compared daptomycin and vancomycin for MRSA bloodstream infections in Veterans Health Administration patients.¹³ Patients remained hospitalized until response or microbiological failure, which required an additional 14 days of salvage treatment.¹³ Patients who were discharged received OPAT for 21 days.¹³ Primary outcomes measured were microbiological failure within the first 7 days of treatment and ADE-related treatment failure after 7 days of treatment added together as a composite.¹³ Cost-effectiveness was analyzed using incremental cost-effectiveness ratios (ICER) with a WTP threshold of \$40,000 to avoid 1 clinical failure.¹³ In the 4-week and 6-week treatment analyses, daptomycin was a more expensive and effective than vancomycin.¹³ A probabilistic sensitivity analysis was conducted using 10,000 iterations via a Monte-Carlo simulation with varying parameters of the stratified primary endpoints demonstrating that at a \$40,000 WTP threshold, daptomycin, vancomycin, and other treatments were favored 50%, 31%, and 19% of the time respectively.¹³ When the WTP is varied, daptomycin was favored over vancomycin most of the time at any WTP >\$15,000, significantly lower than the cost a vancomycin failure (\$40,000) has on the health care continuum.¹³ Some limitations of this analysis are the predominantly male population and the costs used for this study, which are comparable to 340B drug prices to which only a small group of health care facilities have access. The direct drug cost savings, particularly on daptomycin, would be substantial and could impact this analysis if applied to other health systems or OPAT providers. Table 1 lists the studies analyzed and provides an overview of the data.

Discussion

From the approval of daptomycin in 2003, it can be determined that it is non-inferior to vancomycin for susceptible infections. However, when looking at the overall effectiveness of treatment, daptomycin had a much higher clinical success rate due to better tolerability, lower rate of therapy-ending ADE,

shorter infusion time, less frequent dosing, and ease of dosing leading to higher patient satisfaction, mainly when the OPAT setting was included in the analysis. The one clinical area where the data does not strongly favor daptomycin for effectiveness is for less severe infections such as ABSSSI or urinary tract infection (UTI). The reasons for this are evident as lower doses and shorter treatment durations significantly decrease the likelihood of a therapy-ending ADE or clinical failure for vancomycin. In addition, patient satisfaction is less likely to be a barrier as the shorter duration of treatment would impact a patient's life for a shorter period. Since this would lead to a lower rate of treatment failure for vancomycin, the cost-benefit profile would favor vancomycin and make it the superior agent for use in the short term, less severe infections.

The 2 areas that were up for debate prior to this analysis were the antimicrobial stewardship angle and the total cost of treatment for severe infections requiring higher doses of vancomycin and a longer treatment timeline. The article by *Mahoney et al.* addresses stewardship illustrating that the focus for antimicrobial stewardship in OPAT is patients taking a drug correctly and completing therapy as those can also impact antimicrobial resistance.¹⁶ From a total cost of treatment standpoint, the data for longer treatment courses may favor daptomycin for OPAT. *Vu et al.* stated that daptomycin is favored more often than other agents against MRSA at a WTP of \$15,000.¹³ Considering the WTP to avoid a vancomycin-induced AKI is about \$40,000, this makes a compelling case for the use of daptomycin.

There are some limitations to the available data to make a concrete determination of superiority. First, there is no data on vancomycin-induced AKI strictly in the OPAT setting. There are theoretical reasons why it could be higher in the OPAT vs. inpatient setting, but there are no studies focusing on this specifically. With that data point, the rate can be assumed from prior studies, most of which took place in the institutional setting. Second, all these studies were done with trough-based dosing of vancomycin. AUC-based dosing has shown to decrease the risk of AKI by 50% which could significantly change the treatment failure rate of vancomycin due to ADE.¹¹ Finally, a cost-benefit analysis would also need to be done on Bayesian software, an often-used method for AUC calculations. *Jeffres* noted that a pharmacist,

TABLE 1 | Overview of the Reviewed Studies

Author	Title	Study Sample Size	Summary
<i>Maraolo et al.</i>	Daptomycin versus vancomycin for the treatment of methicillin-resistant <i>Staphylococcus aureus</i> bloodstream infection with or without endocarditis: a systematic review and meta-analysis	1,226 patients, 554 vs. 672 in daptomycin vs. vancomycin, respectively	Risk of clinical failure of Daptomycin vs. Vancomycin = OR 0.58. Discontinuation of medication due to adverse effects of Daptomycin vs. Vancomycin = OR 0.15. Mortality of Daptomycin vs. Vancomycin patients = OR 0.73 (not statistically significant)
<i>Nathwani D. via CORE trial</i>	Developments in outpatient parenteral antimicrobial therapy (OPAT) for gram-positive infections in Europe, and the potential impact of daptomycin	1,160 patients treated with daptomycin for susceptible infections	Clinical success rate inpatient = 86.3%, Clinical success rate outpatient = 94.6%
<i>Rehm et al.</i>	Community-based outpatient parenteral antimicrobial therapy (Copat) for <i>Staphylococcus aureus</i> bacteraemia with or without infective endocarditis: analysis of the randomized trial comparing daptomycin with standard therapy	200 patients, 103 daptomycin, 97 with standard of care (SoC)	Daptomycin clinical success rate = 90%. Semi-synthetic penicillin or vancomycin + gentamicin (SoC) = 83%. Infection relapse rate: daptomycin = 3.9%, SoC = 15.5%. Mortality rate 6 weeks after completion of therapy: daptomycin = 3.9%, SoC = 18.6%. Completion rate of daptomycin vs. vancomycin = 90.3% vs. 45.4%
<i>Seaton et al.</i>	Daptomycin for outpatient parenteral antibiotic therapy: A European Registry experience (EU-CORE)	550 patients received daptomycin OPAT	The overall clinical success of daptomycin over susceptible infections for OPAT = 89%
<i>Shrestha et al.</i>	Adverse events, health care interventions, and health care utilization during home infusion therapy with daptomycin and vancomycin: a propensity score-matched cohort study	119 daptomycin, 357 vancomycin	ADE rate 3.2 vs. 7.7 events per 1,000 OPAT days, 5.6 vs. 27.1 antimicrobial interventions per 1,000 OPAT days for daptomycin vs. vancomycin, respectively
<i>Schrank et al.</i>	A retrospective analysis of adverse events among patients receiving daptomycin versus vancomycin during outpatient parenteral antimicrobial therapy	105 daptomycin, 312 vancomycin	ADE leading to change or early discontinuation of treatment 7.6% vs. 19% daptomycin vs. vancomycin, respectively. aOR = 3.71 for the incidence of ADE for vancomycin over daptomycin
<i>Patel et al.</i>	Economic burden of inpatient and outpatient antibiotic treatment for methicillin-resistant <i>Staphylococcus aureus</i> complicated skin and soft-tissue infections: a comparison of linezolid, vancomycin, and daptomycin.	Cost per patient based on 7 to 14 days of treatment	Total cost of treatment: daptomycin = \$13,612, vancomycin = \$11,096. Gain in QALYs for daptomycin over vancomycin-treated patients = 0.001 QALY
<i>Vu et al.</i>	Exploratory cost-effectiveness analysis for treatment of methicillin-resistant <i>Staphylococcus aureus</i> bloodstream infections: Is linezolid or daptomycin favored over vancomycin?	Cost per patient for 4 and 6 week regimens with probabilistic sensitivity analysis, including 10,000 iterations via Monte-Carlo simulation	Daptomycin dominated vancomycin at 4 and 6 weeks of treatment. Sensitivity analysis: Daptomycin, vancomycin, and linezolid were favored in 50%, 31%, and 17% of 4-week probabilistic iterations, respectively, at \$40,000 WTP.

on average, takes about 40 minutes to evaluate patients regarding pharmacokinetic evaluation, interpret results, and follow-up with the patient.⁹ The possible decrease in provider time cost vs. the cost of using the software would have to be assessed to see how this would affect the total cost of treatment.

Many of the cost analyses conducted either occurred prior to the introduction of generic daptomycin to the market or were completed in a setting where the cost does not reflect what most health systems or purveyors of OPAT would pay. Therefore, a study using non-government priced drugs would need to be performed with costs extrapolated to the present day to best quantify if there are any differences. In addition, the acute nature of treatment with these drugs makes pharmacoeconomic analysis, such as cost-effectiveness or cost-utility analysis, difficult as these analyses are usually performed on chronic conditions with a long duration of therapy. When *Patel et al.* attempted a cost-effectiveness analysis on vancomycin and daptomycin for MRSA ABSSSI, they showed a difference of 0.001 QALY (8.8 quality-adjusted life hours), which is not likely to sway an argument toward one medication or another.²³ Finally, there are no studies analyzing the societal costs of using vancomycin in the OPAT setting. With more frequent, longer dosing requirements, up to biweekly lab monitoring, and the possibility of renal failure, which could cause an additional hospitalization and longer courses of antimicrobial treatment, this can impact the patient's time away from work decreasing their productivity and productivity of family members supporting the patient during their treatment.

Conclusion

With an efficacy rate that is non-inferior to vancomycin, an effectiveness rate that may be superior to vancomycin in the OPAT setting, a lower risk of ADE, simplified lab requirements and dosing, and a likely cost-benefit to the health care continuum for longer-term therapy, daptomycin may be superior to vancomycin for use in severe infections in the OPAT setting. However, further studies are needed in the OPAT setting to address rate of ADE and costs.

Funding: No funding was received for this manuscript

References

1. Global Market Insights Inc. 2022. Home Infusion Therapy Market Size, Forecast Report 2021-2027. [online] Available at: <<https://www.gminsights.com/industry-analysis/home-infusion-therapy-market-report>> [Accessed 1 July 2022].
2. Accessdata.fda.gov. 2022. [online] Available at: <https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/060180s047lbl.pdf> [Accessed 10 July 2022].
3. Cano EL, Haque NZ, Welch VL, et al. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP Database. *Clin Ther.* 2012;34(1):149-157.
4. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clin Infect Dis.* 2011;52(3):e18-55.
5. Bamgbola O. Review of vancomycin-induced renal toxicity: an update. *Ther Adv Endocrinol Metab.* 2016;7(3):136-147.
6. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant staphylococcus aureus infections: efficacy and toxicity. *Arch Intern Med.* 2006;166(19):2138.
7. Rochesterhomeinfusion.com. 2022. Anti-Infectives | IV Therapy Services | In Home IV Treatment. [online] Available at: <<https://www.rochesterhomeinfusion.com/services/anti-infective.html>> [Accessed 2 July 2022].
8. Shrestha NK, Mason P, Gordon SM, et al. Adverse events, healthcare interventions and healthcare utilization during home infusion therapy with daptomycin and vancomycin: a propensity score-matched cohort study. *Journal of Antimicrobial Chemotherapy.* 2014;69(5):1407-1415
9. Jeffres MN. The whole price of vancomycin: toxicities, troughs, and time. *Drugs.* 2017;77(11):1143-1154.
10. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother.* 2013;57(2):734-744.
11. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, Mueller BA, Pai MP, Wong-Beringer A, Rotschafer JC, Rodvold KA, Maples HD, Lomaestro BM. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm.* 2020 May 19;77(11):835-864. doi: 10.1093/ajhp/zxaa036. PMID: 32191793.
12. Lee BV, Fong G, Bolaris M, et al. Cost-benefit analysis comparing trough, two-level AUC and Bayesian AUC dosing for vancomycin. *Clin Microbiol Infect.* 2021;27(9):1346.e1-1346.e7.
13. Vu, M., Smith, K.J., Aspinall, S.L. et al. Exploratory Cost-Effectiveness Analysis for Treatment of Methicillin-Resistant Staphylococcus aureus Bloodstream Infections: Is Linezolid or Daptomycin Favored Over Vancomycin? *Clin Drug Investig* 41, 885–894 (2021). <https://doi.org/10.1007/s40261-021-01077-8>
14. Merck.com. 2022. [online] Available at: <https://www.merck.com/product/usa/pi_circulars/c/cubicin/cubicin_pi.pdf> [Accessed 2 July 2022].
15. Schrank GM, Wright SB, Branch-Elliman W, LaSalvia MT. A retrospective analysis of adverse events among patients receiving daptomycin versus vancomycin during outpatient parenteral antimicrobial therapy. *Infect Control Hosp Epidemiol.* 2018;39(8):947-954.

16. Mahoney, M.V., Childs-Kean, L.M., Khan, P. et al. Recent Updates in Antimicrobial Stewardship in Outpatient Parenteral Antimicrobial Therapy. *Curr Infect Dis Rep* 23, 24 (2021).
17. Maraolo AE, Giaccone A, Gentile I, Saracino A, Bavaro DF. Daptomycin versus vancomycin for the treatment of methicillin-resistant staphylococcus aureus bloodstream infection with or without endocarditis: a systematic review and meta-analysis. *Antibiotics (Basel)*. 2021;10(8):1014.
18. Nathwani D. Developments in outpatient parenteral antimicrobial therapy (Opat) for Gram-positive infections in Europe, and the potential impact of daptomycin. *J Antimicrob Chemother*. 2009;64(3):447-453.
19. Rehm S, Champion M, Katz DE, Russo R, Boucher HW. Community-based outpatient parenteral antimicrobial therapy (Copat) for Staphylococcus aureus bacteraemia with or without infective endocarditis: analysis of the randomized trial comparing daptomycin with standard therapy. *J Antimicrob Chemother*. 2009;63(5):1034-1042.
20. Seaton RA, Gonzalez-Ramallo VJ, Prisco V, et al. Daptomycin for outpatient parenteral antibiotic therapy: a European registry experience. *Int J Antimicrob Agents*. 2013;41(5):468-472.
21. Neiman AB, Ruppert T, Ho M, et al. CDC Grand Rounds: Improving Medication Adherence for Chronic Disease Management — Innovations and Opportunities. *MMWR Morb Mortal Wkly Rep* 2017;66. DOI: <http://dx.doi.org/10.15585/mmwr.mm6645a2>.
22. Wu KH, Sakoulas G, Geriak M. Vancomycin or daptomycin for outpatient parenteral antibiotic therapy: does it make a difference in patient satisfaction? *Open Forum Infectious Diseases*. 2021;8(8):ofab418.
23. Patel D, Stephens J, Gao X, Verheggen, Shelbaya A, Haider S. Economic burden of inpatient and outpatient antibiotic treatment for methicillin-resistant Staphylococcus aureus complicated skin and soft-tissue infections: a comparison of linezolid, vancomycin, and daptomycin. *CEOR*. Published online September 2013:447.