Journal of Pharmacy and Pharmacology 4 (2016) 241-247
doi: 10.17265/2328-2150/2016.06.001

Risk Factors for Failure of OPAT (Outpatient Parenteral Antimicrobial Therapy) in Veterans with *Staphylococcus aureus* Bacteremia

John J. Veillette[1], Leslie Bittner[1], Marion J. Skalweit[2,3], Usha Stiefel[2,3], Christopher J. Burant[4,5], Amy A. Hirsch[1,3,4] and Sharanie Sims[1]

1. Pharmacy Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center (LSCDVAMC), Cleveland, OH, USA

2. Medicine Service, LSCDVAMC, Cleveland, OH, USA

3. Case Western Reserve University, School of Medicine, Cleveland, OH, USA

4. Cleveland Geriatric Research Education and Clinical Center (GRECC), LSCDVAMC, Cleveland, OH, USA

5. Case Western Reserve University, Frances Payne Bolton School of Nursing, Cleveland, OH, USA

Abstract: To identify risk factors for failure of OPAT (outpatient parenteral antimicrobial therapy) among veterans with SAB (*Staphylococcus aureus* bacteremia), a retrospective review was conducted of all patients receiving OPAT for SAB between 01/2011-09/2013 at a large, tertiary-care VA (Veterans' Affairs) medical center. Treatment failure was defined as incomplete therapy, therapy extension, infection relapse, or hospital admission or surgical intervention within 60 days of therapy completion. Of 118 SAB patients treated with OPAT, 101 met inclusion criteria. Treatment failure occurred in 36 (35.6%) patients. In multivariate analysis, heart failure (OR 3.67; CI 1.13-12.0), previous OPAT (OR 14.1; CI 2.02-97.8), immunosuppression (OR 10.5; CI 1.74-63.3), and treatment with daptomycin (OR 9.56; CI 1.89-48.4) were independently associated with failure. A trend toward lower failure rates was seen in the community living center, a VA long-term care facility possessing its own infectious diseases consultation service. In veterans with SAB, specific health factors were associated with higher rates of OPAT failure. Given the morbidity and cost of SAB treatment failures, similar analyses may benefit other large OPAT programs to optimize the selection of patients and settings in which successful treatment will most likely occur.

Key words: Risk factors, failure, OPAT, *Staphylococcus aureus,* bacteremia.

1. Introduction

SAB (*Staphylococcus aureus* bacteremia) is a serious infection requiring prolonged courses of intravenous antibiotic therapy [1, 2]. OPAT (outpatient parenteral antimicrobial therapy) is frequently used to complete this treatment and has several advantages including cost savings, decreased risk of hospital-acquired infection, and increased patient autonomy [3]. While OPAT is generally considered safe and effective, recent studies have reported failure rates in patients with SAB from 13-31% suggesting opportunities for process improvement [4, 5]. Certain risk factors in these studies, such as heart failure and chronic kidney disease, have been associated with treatment failure. Similarly, we hypothesized that specific risk factors for OPAT failure exist in our veteran patient population.

The primary objective for the study was to identify risk factors for OPAT treatment failure so that the process of patient selection, determination of disposition, and treatment could be improved in our medical center. Additionally, we sought to define our OPAT failure rate in SAB patients and to compare outcomes between outpatient treatment settings.

Corresponding author: John J. Veillette, Pharm.D., BCPS, Loma Linda University School of Pharmacy, Shryock Hall, Room 234, 24745 Stewart Street, Loma Linda, California, USA 92350, E-mail: john.veillette@gmail.com.

2. Materials and Methods

2.1 Inclusion/Exclusion Criteria

Approval for the study was obtained from the Institutional Review Board at the LSCDVAMC (Louis Stokes Cleveland Department of Veterans Affairs Medical Center) prior to study commencement. This was a retrospective review utilizing the medical center's electronic OPAT database. Patients who received OPAT for an episode of SAB from any source between January 2011 and September 2013 were included in the study. Patients were excluded if bacteremic with more than one organism or if enrolled in the spinal cord rehabilitation program at the medical center. As spinal cord patients receive around the clock nursing care, the authors felt that this was more reflective of inpatient than outpatient treatment. Patients receiving OPAT with suppressive or palliative rather than curative intent were also excluded.

2.2 Outcomes

The primary outcome of the study was treatment failure, which was defined as incomplete therapy, unplanned intravenous or oral therapy extension, infection relapse, or hospital admission or surgical intervention related to initial infection within 60 days of therapy completion. Data was collected on patient demographics, comorbidities, and OPAT regimen to determine potential risk factors for treatment failure. OPAT outcomes were also compared across different treatment settings when patients were discharged to home, to a community skilled nursing facility, or to the VA CLC (community living center), a skilled nursing facility attached to the medical center possessing its own infectious diseases consult service.

2.3 Definitions of Comorbidities

In addition to documentation in progress notes or the patient's problem list in the electronic medical record, the following definitions were utilized to classify patients as having or not having specific risk factors: HFrEF or HFpEF (heart failure defined as either reduced or preserved ejection fraction) noted on most recent echocardiogram; chronic kidney disease defined as baseline eGFR < 60 mL/min/m^2 per patient medical record, or status-post kidney transplant; previous OPAT defined as OPAT for SAB prior to the study period or OPAT for alternative indication prior to treatment for SAB during the study period; and immunosuppression defined as taking maintenance transplant anti-rejection medications, TNF (tumor necrosis factor)-α inhibitors, DMARDs (disease-modifying anti-rheumatic drugs), azathioprine, methotrexate, IL-1 antagonists, chronic steroids (> 3 months at ≥ 40 mg prednisone/day equivalent), HIV with CD4 count < 250, or cancer status-post chemotherapy within the last 6 months.

2.4 Statistics

Three types of analyses were used: Student's t-test, chi-squared test, and multivariate logistic regression. As the dependent variable of interest (treatment failure) is dichotomous, logistic regression analysis was used to identify the odds ratios from a set of predictors. Since the data were normally distributed, chi-squared test and Student's t-test were used to identify significant differences between success and failure groups with significance set at $\alpha = 0.05$. Risk factors found to be significantly different or close to significant with a p-value < 0.10 were included in a multivariate logistic regression to identify the strongest set of predictors of treatment failure while controlling for each predictor's influence on the others. There were no violations of the assumptions (e.g., influential cases, multicollinearity, adequate variance) for logistic regression.

2.5 Details of Ethical Approval for the Study

Approval from the Institutional Review Board at LSCDVAMC was obtained on December 20, 2011 prior to study commencement.

The IRB approval number for the study is 11082-H51.

3. Results

3.1 Included Patients

Of 118 OPAT episodes for SAB between January 2011 and September 2013, 101 met inclusion criteria, which constituted a total of 98 unique patients. Selected baseline characteristics are shown in Table 1. All sources of bacteremia were included in the study with the most common being skin and soft tissue or bone and joint infections (60/101 patients). Ten patients had SAB secondary to line infection, and fourteen had definite endocarditis as defined by the modified Duke criteria [6]. Other sources of bacteremia were due to urinary tract infection, pneumonia, or unknown source.

Comorbidities were common among included patients prior to OPAT therapy (see Table 2). 85/101 patients (84.1%) had at least 1 of the following—diabetes, chronic kidney disease, coronary artery or peripheral vascular disease, heart failure, or obesity. 45 patients (44.6%) had either a history of or active hematologic/oncologic disease. 25 patients (24.8%) had a prosthetic heart valve or history of other hardware such as hip or knee replacement, and 12 patients (11.9%) had a history of SAB prior to the study period.

Table 1 Baseline patient characteristics.

	Number of patients (%) (n = 101)
Gender, male	95 (94%)
Race Caucasian	73 (72%)
African American	24 (24%)
Unknown	4 (4%)
Age (years), mean ± SD	64 ± 11
Distance from medical center (miles), mean ± SD	38.9 ± 34.4
Time to negative blood culture (days), mean ± SD	3.52 ± 2.80

Table 2 Risk Factors for treatment failure.

	Success (n = 65)	Failure (n = 36)	Univariate Analysis		Multivariate Regression	
			Odds ratio (95% CI)	*P-value*	*Odds ratio (95% CI)*	*P-value*
Heart Failure	13 (44.8%)	16 (55.2%)	3.20 (1.31-7.83)	0.009	3.67 (1.13-12.0)	0.031
Chronic Kidney Disease	24 (53.3%)	21 (46.7%)	2.39 (1.04-5.49)	0.038	1.47 (0.49-4.40)	0.487
Previous OPAT	3 (23.1%)	10 (76.9%)	7.95 (2.02-31.3)	0.001	14.1 (2.02-97.8)	0.008
Immunosuppression	2 (22.2%)	7 (77.8%)	7.60 (1.32-56.8)	0.006	10.5 (1.74-63.3)	0.010
Diabetes Mellitus	40 (65.6%)	21 (34.4%)	0.87 (0.38-2.01)	0.752	--	
CAD / PVD	31 (60.8%)	20 (39.2%)	0.73 (0.32-1.65)	0.573	--	
Hematologic/oncologic disorder	25 (58.1%)	18 (41.9%)	1.60 (0.70-3.64)	0.261	--	
Psychiatric disorder	37 (66.1%)	19 (33.9%)	1.18 (0.52-2.68)	0.688	--	
Obesity (BMI ≥ 30 kg/m^2)	28 (58.3%)	20 (41.7%)	1.65 (0.73-3.75)	0.229	--	
Ethanol/tobacco abuse	25 (61.0%)	16 (39.0%)	0.78 (0.34-1.78)	0.558	--	
Substance abuse	13 (65.0%)	7 (35.0%)	1.04 (0.37-2.89)	0.947	--	
History of non-compliance	13 (65.0%)	7 (35.0%)	0.75 (0.26-2.19)	0.601	--	
Prosthetic valve or other hardware	16 (64.0%)	9 (36.0%)	0.98 (0.38-2.51)	0.965	--	
History of SAB prior to study period	5 (41.7%)	7 (58.3%)	2.90 (0.85-9.90)	0.080	0.83 (0.13 – 5.39)	0.848
MRSA	30 (62.5%)	18 (37.5%)	1.17 (0.52-2.64)	0.711	--	
Vancomycin MIC >1	3 (60.0%)	2 (40.0%)	0.82 (0.13-5.17)	0.834	--	
Treatment with Daptomycin	3 (33.3%)	6 (66.7%)	4.13 (0.97-17.8)	0.042	9.56 (1.89-48.4)	0.006

CI—confidence interval, CAD—coronary artery disease, PVD—peripheral vascular disease, BMI—body mass index, SSTI—skin and soft tissue infection, BJI—bone and joint infection, MRSA—methicillin-resistant *Staphylococcus aureus*, MIC—minimum inhibitory concentration

3.2 Interventions

All patients were evaluated by an infectious disease specialist in the medical center prior to receiving OPAT. Furthermore, all patients received periodic monitoring and follow-up from an infectious disease specialist during and at the conclusion of their OPAT course. All patients were initiated on IV antibiotics in the hospital prior to discharge. The majority of patients with bacteremia due to MRSA received vancomycin (79.2%), while most patients with MSSA bacteremia received either ceftriaxone or cefazolin (47.2% and 35.8% of patients respectively). The mean OPAT treatment duration was 4.95 weeks.

3.3 Outcomes

36 out of 101 episodes (35.6%) met the composite definition for treatment failure. Reasons for treatment failure were primarily unplanned extension of IV or oral therapy (29/36), readmission related to initial infection (28/36), and relapse of infection (24/36). Fourteen patients required unplanned surgical intervention (all for concomitant bone and joint infections), of which five were amputations. Thirteen patients failed to complete intravenous therapy, of which four were due to adverse drug reactions [3-acute kidney injury or renal failure; 1-self-discontinuation due to rash]. Two patients died during the study period —one due to culture-negative septic shock during OPAT and one due to complications from hepatocellular carcinoma shortly after completion of OPAT.

3.4 Univariate Analysis

No significant differences were found between success and failure groups for average age (65 versus 62 years), average distance from the medical center (36 versus 42 miles), or time to negative blood culture (3.8 versus 2.9 days, respectively). Similarly, no differences in outcomes were seen based on race or gender between the groups.

Chi-squared analysis revealed significant differences between success and failure groups for patients with heart failure, chronic kidney disease, or immunosuppression (Table 2). A significant association with failure was also found for patients who received previous OPAT or who were treated with daptomycin. No other antimicrobial agents were predictive of treatment failure. No significant differences were found for the causative organism (MRSA vs. MSSA), vancomycin MIC > 1 mg/L, or for the source of bacteremia except those due to an unknown source, which was associated with treatment success. Additional comparisons of baseline characteristics between success and failure groups may be found in Table 2.

Of the two patients with immunosuppression classified as an OPAT success, one patient was taking ustekinumab for psoriatic arthritis and one was on maintenance methotrexate for ulcerative colitis. The seven classified as OPAT failures had the following characteristics: three with rheumatoid arthritis—one taking prednisone and azathioprine daily, one taking etanercept once weekly, and one with concomitant psoriasis taking weekly methotrexate and daily leflunomide; two status-post transplant—one heart and one kidney transplant on immune suppression; one with recurrent polyarticular gout treated with steroids and anakinra; and one with AIDS with a CD4 count of 82, Hodgkin's lymphoma and rectal carcinoma with recent chemotherapy prior to OPAT.

Among OPAT treatment settings, failure rates were lowest in the VA community living center (6/25, 24.0%) and highest in skilled nursing facilities (10/23, 43.5%), although these differences were not found to be statistically significant. Of 53 patients treated with OPAT in the home setting, 20 failed therapy (37.7%).

3.5 Multivariate Analysis

Of the variables identified as significant or close to significant ($p < 0.10$) on univariate analysis, heart failure, previous OPAT, immunosuppression, and

treatment with daptomycin were independently associated with treatment failure on multivariate logistic regression (Table 2).

4. Discussion

Previous studies have addressed risk factors for failure of OPAT in other infections including endocarditis and bone and joint infections [5, 7]; however, risk factors specifically in SAB are largely unknown. This is an important treatment question as SAB is associated with a high cost burden on health care systems and is associated with considerable morbidity and mortality [2, 4]. We used broad criteria for treatment failure, which are consistent with definitions outlined in previous studies, current BSAC (British Society for Antimicrobial Chemotherapy) best practice recommendations, and IDSA (Infectious Diseases Society of America) guidelines for OPAT [3-5, 8]. While these criteria likely overestimated the number of treatment failures in our study, the failure rate of 35.6% was similar to previous OPAT studies evaluating patients with SAB or SAB/IE (range 13-31%) [4, 5].

Risk factors for failure identified in this study are largely consistent with previous studies as well. Duncan and colleagues identified either heart failure or CKD as risk factors for OPAT failure in patients with SAB/IE (pooled OR 7.48, 95% CI 2.52-22.21) [5]. Although only significant on univariate analysis, results from this study and from the Duncan study suggest that CKD warrants further investigation as a potential risk factor for OPAT failure in SAB. Immunosuppression is a well-documented risk factor for developing SAB and for recurrence [2, 9-11]. Therefore, it is logical that these patients may be at increased risk for treatment failure as well.

While previous OPAT was significantly associated with failure on multivariate analysis, this relationship may not be causal in nature. It is likely that this represents both the complexity of veterans treated in our medical center and the high relapse rates seen in *S. aureus* infections. However, this finding also suggests opportunity for improvement of our OPAT program and further validates the study rationale stated previously.

One finding in contrast to those of previous studies was the independent association between daptomycin and treatment failure. Daptomycin is commonly used for OPAT due to convenient once daily dosing in patients with CrCl $\geq$ 30mL/min, rapid bactericidal activity, and comparable efficacy to standard therapy with vancomycin for SAB and SAB/IE [4, 9, 12]. In our study 6 of 9 patients receiving daptomycin failed therapy. Of these, all were switched from vancomycin to daptomycin during their inpatient stay for one of the following reasons: progression of infection (2 patients), adverse reaction (2 patients), resistance (1 patient) and inability to reach therapeutic vancomycin levels (1 patient). Treatment failures may have resulted from the pathogenicity of the organism and infection severity rather than due to the agent itself, although an alternative explanation could be daptomycin dosing. Five of six patients failing daptomycin received 6 mg/kg daily, and there is some evidence to suggest that higher doses (8-10 mg/kg daily) may be warranted in serious gram positive infections [1, 13]. However, despite these findings in our small study, we still consider daptomycin to be a useful agent in OPAT for SAB.

These data do have several limitations. Determining with certainty the effect of each risk factor on treatment outcomes is difficult considering that patients were not randomized and that the number of patients within each category was relatively small. While some risk factors were significantly associated with failure on multivariate analysis, it is possible that additional factors could be identified with a larger sample size. Furthermore, baseline data was not collected on inpatient length of stay and duration of IV antibiotics prior to discharge, which could have altered OPAT treatment outcomes. Data collection was limited to the VA electronic medical record; therefore, admissions to

any outside facility were not captured in the data set unless recorded by a VA provider. While previous studies have assessed outcomes up to 12 months after OPAT, patients were followed for 60 days after OPAT in our study. The 60 day time frame was included in our composite definition for treatment failure as we felt that this would be most reflective of the success or failure of the isolated OPAT course. However, this approach may have also resulted in the omission of relevant outcomes data, which were not gathered beyond 60 days of OPAT completion. To our knowledge this study is the largest to date addressing risk factors for failure of OPAT in SAB; however, the number of cases identified was relatively small and larger prospective studies are still needed.

Our study does make an important comparison of outcomes between OPAT treatment settings, but analysis of these outcomes is limited by selection bias. Patients unfit to be treated at home (due to poor functional status, severity of illness, lack of caregiver support, etc.) will likely be discharged to a skilled facility rather than home. Therefore, it is unsurprising that a non-significant trend toward higher failure rates was found in patients treated at skilled nursing facilities. Conversely, this makes the trend toward greater success rates in the VA CLC more meaningful in that closer monitoring of OPAT by an infectious disease specialist may have a positive impact on treatment outcomes in these complicated patients.

5. Conclusions

In summary, in a complex veteran population, OPAT failure rates for SAB were consistent with those previously reported in the literature. Although specific health factors such as heart failure, immunosuppression, and previous OPAT were associated with higher rates of failure in our study, these are not contraindications to OPAT so long as risk factors are fully assessed and the treatment setting and monitoring frequency are adjusted accordingly. Given the morbidity and cost of SAB treatment failures, similar analyses may benefit other large OPAT programs, in order to prospectively optimize the local selection of patients and settings in which successful treatment will most likely occur.

Acknowledgements

We would like to thank the GRECC (Geriatric Research Education and Clinical Center) at the Cleveland VA medical center for its continued support and assistance with biostatistical analysis

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The study was conducted as a routine part of our work and the work of the organization.

References

[1] Liu, C., Bayer, A., Cosgrove, S. E., Daum, R. S., Fridkin, S. K., Gorwitz, R. J. et al. 2011. "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.* 52 (3): e18-55.

[2] Naber, C. K. 2009. "*Staphylococcus aureus* Bacteremia: Epidemiology, Pathophysiology, and Management Strategies." *Clin. Infect. Dis*. 48 Suppl 4: S231-7.

[3] Tice, A. D., Rehm, S. J., Dalovisio, J. R., Bradley, J. S., Martinelli, L. P., Graham, D. R. et al. 2004. "Practice Guidelines for Outpatient Parenteral Antimicrobial Therapy. IDSA Guidelines." *Clin. Infect. Dis.* 38 (12): 1651-72.

[4] Rehm, S., Campion, M., Katz, D. E., Russo, R., and Boucher, H. W. 2009. "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* 63: 1034-42.

[5] Duncan, C. J., Barr, D. A., Ho, A., Sharp, E., Semple, L., and Seaton, R. A. 2013. "Risk Factors for Failure of Outpatient Parenteral Antibiotic Therapy (OPAT) in Infective Endocarditis." *J. Antimicrob Chemother* 68 (7): 1650-4.

[6] Li, J. S., Sexton, D. J., Mick, N., Nettles, R., Fowler, V. G. Jr., Ryan, T. et al. 2000. "Proposed Modifications to the

Duke Criteria for the Diagnosis of Infective Endocarditis." *Clin. Infect. Dis.* 30: 633-8.

[7] Bittner, L., Sims, S., Hirsch, A., Stiefel, U., and Skalweit, M. 2012. "Management of Bone and Joint Infections (BJI) with Outpatient Parenteral Antimicrobial Therapy (OPAT) in a Veteran Population: Risk Factors for Failure of Therapy." Presented at the 50th Infectious Diseases Society of America Annual Meeting, San Diego, CA.

[8] Chapman, A. L., Seaton, R. A., Cooper, M. A., Hedderwick, S., Goodall, V., Reed, C. et al. 2012. "Good Practice Recommendations for Outpatient Parenteral Antimicrobial Therapy (OPAT) in Adults in the UK: A Consensus Statement." *J. Antimicrob Chemother* 67 (5): 1053-62.

[9] Fowler, V. G. Jr., Boucher, H. W., Corey, G. R., Abrutyn, E., Karchmer, A. W., Rupp, M. E. et al. 2006. "Daptomycin Versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*." *N. Engl. J. Med.* 355: 653-65.

[10] Mitchell, D. H., and Howden, B. P. 2005. "Diagnosis and Management of *Staphylococcus aureus* Bacteraemia." *Intern. Med. J.* 35 (Suppl 2): S17-24.

[11] Kreisel, K., Boyd, K., Langenberg, P., and Roghmann, M. C. 2006. "Risk Factors for Recurrence in Patients with *Staphylococcus aureus* Infections Complicated by Bacteremia." *Diagn. Microbiol. Infect. Dis.* 55: 179-84.

[12] Cubicin® (Daptomycin for Injection) Current Prescribing Information. Accessed June 22, 2014. http://cubicin.com/pdf/PrescribingInformation.pdf.

[13] Kullar, R., Davis, S. L., Levine, D. P., Zhao, J. J., Crank, C. W., Segreti, J. et al. 2011. "High-Dose Daptomycin for Treatment of Complicated Gram-Positive Infections: A Large, Multicenter, Retrospective Study." *Pharmacotherapy* 31 (6): 527-36.