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BRIEF REPORT

Treatment of Staphylococcal Device Infections: Synergistic Daptomycin With Ceftaroline Versus Rifampin-Adjunct Therapy

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Medical device infections are a serious healthcare concern with increased morbidity, mortality up to 25%, and costs ranging from $1000 to $50 000 associated with each case [1]. The most common causative organism in these infections is *Staphylococcus*, which is a frequent commensal organism that may colonize devices during implantation. Physical removal of the device and antibiotic therapy are the primary methods used to treat device infections, although clinical success is most likely to be achieved if a combination of both approaches is implemented [2]. Certain patients are not candidates for surgical intervention due to substantial risk for complications; therefore, in these cases, antibiotic therapy alone is used, often requiring indefinite suppression. Increasing rates of antibiotic resistance and emergence of refractory infections are common treatment considerations with all infections; however, device infections pose additional therapeutic challenges if source control is not achieved.

As recommended by the Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children, rifampin is frequently combined with standard therapy of vancomycin or antistaphylococcal beta-lactams in device infections, particularly prosthetic valve endocarditis [2]. This application of rifampin is due to its ability to penetrate biofilms and maintain activity against both dividing and stationary cells [2, 3]. Rifampin use is associated with risks of hepatotoxicity, rifampin resistance, and CYP450-related drug interactions, notably with warfarin and direct oral anticoagulants, which are often concomitantly prescribed in patients with prosthetic devices [4]. For these reasons, certain patients may be inappropriate candidates for rifampin-adjunct (RIF-Adj) therapy; therefore, it is important to identify alternative antibiotic regimens to treat these patient populations.

As a potential alternative, daptomycin with ceftaroline (DAP/CFT) has been used successfully for salvage treatment of refractory or relapsing infections caused by staphylococci due to synergy [5, 6]. Data to support this combination for staphylococcal device infections are limited, and a substantial cost difference must be considered if it were to be used. Therefore, the purpose of this observational study is to compare clinical outcomes of synergistic DAP/CFT to RIF-Adj therapy in the treatment of staphylococcal device infections.

METHODS

Design Overview

This was a single-center retrospective observational cohort study which compared the clinical success of using DAP/CFT versus RIF-Adj for the treatment of staphylococcal device infections at a 500-bed community teaching hospital. Drug administration reports for rifampin and ceftaroline were retrieved from the electronic medical record for the time-period of July 1, 2016 to June 30, 2018. The research was approved by the Institutional Review Board in September 2018.

Study Cohort

Eligible inpatients were aged 18 years or older with a documented staphylococcal device infection that was treated with an antibiotic combination of DAP/CFT or RIF-Adj during the defined study period. Patients were excluded if the infected device was extracted.

Clinical Outcomes

The primary outcome of clinical success was assessed and compared between patients receiving DAP/CFT and those receiving RIF-Adj for staphylococcal device infections. Clinical success was defined as achieving all 3 criteria of white blood cell normalization (3.3 to $10.5 \times 10^3/\mu L$), sustained defervescence (temperature <38°C), and resolution of all signs and symptoms of infection per chart notes (see Supplementary Material).

Secondary outcomes included in-hospital all-cause mortality, length of stay, infection-related readmission at 30 and 90 days, and duration of antimicrobial combination therapy. Documented adverse drug reactions were also collected: creatinine phosphokinase elevation, transaminitis, peripheral

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eosinophilia, agranulocytosis, leukopenia, and development of nosocomial *Clostridioides difficile* infection during admission.

Statistical Analyses

Categorical variables were presented as the number of cases with corresponding percentages, and continuous variables were presented as the mean and standard deviation or median and interquartile range. The primary outcome of clinical success was analyzed using Fisher's exact test. Secondary outcomes were analyzed using Fisher's exact test for nominal data and Student's *t* test (parametric data) or Mann-Whitney *U* test (nonparametric data) for continuous data. For the primary outcome, 310 patients would need to be included in the final analysis to detect a 10% difference with an alpha of 0.05 and 80% power, assuming a clinical success rate of 80% in the RIF-Adj group.

RESULTS

Patient Characteristics

Of the 153 patients identified through drug administration reports for ceftaroline and rifampin during the study period, 116 were excluded for receiving combination therapies aside from DAP/CFT and RIF-Adj or receiving antibiotics for nonstaphylococcal or nondevice-associated infections. Of the remaining 37 patients, 6 and 31 received DAP/CFT and RIF-Adj, respectively, and were included in the study cohort for data analysis. Baseline patient characteristics are presented in Table 1.

Table 1. Baseline Characteristics

Demographics	DAP/CFT (n = 6)	RIF-Adj (n = 31)	*P* Value
Age [years; mean ± SD]	63 ± 19	55 ± 15	.256
ICU admission [patients]	2 (33)	4 (13)	.245
APACHE II score [patients, n (%)]			.067
<20	0	4 (100)	
≥20	2 (100)	0	
CCI score [patients, n (%)]			.371
0–3	2 (33)	19 (61)	
≥4	4 (67)	12 (39)	
Type of device [patients, n (%)]			.157
Cardiac	4 (67)	10 (32)	
Joint	0	11 (36)	
ORIF	2 (33)	10 (32)	
Previously failed antibiotic [patients]	6 (100)	8 (26)	.001
Causative microorganism [patients, n (%)]			<.001
MSSA	0	22 (71)	
MRSA	6 (100)	5 (16)	
CoNS	0	1 (3)	
Other	0	3 (10)	

Abbreviations: APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; CCI, Charlson comorbidity index; CoNS, coagulase-negative staphylococci; DAP/CFT, daptomycin/ceftaroline; ICU, intensive care unit; ORIF, open reduction internal fixation; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; RIF-Adj, rifampin-adjunct; SD, standard deviation.

Six patients required initial treatment in the intensive care unit (ICU): 2 patients from the DAP/CFT group had Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II scores ≥20, whereas the other 4 patients from the RIF-Adj group had APACHE II scores <20. Patients with Charlson comorbidity index scores ≥4 accounted for 67% and 39% of the DAP/CFT and RIF-Adj groups, respectively.

Cardiac device infections comprised the majority (67%) of the DAP/CFT group, whereas type of device was more evenly distributed in patients receiving RIF-Adj. All DAP/CFT patients had previously failed antimicrobial therapy compared with 26% in the RIF-Adj group. *Staphylococcus aureus* was isolated as the primary causative organism in both groups.

Primary Outcomes

No significant differences were demonstrated in the primary outcome of achieving clinical success with DAP/CFT versus RIF-Adj (83% vs 77%, $P = 1.00$) (Table 2).

Secondary Outcomes

No statistically significant differences were noted in secondary outcomes with the exception of length of hospital stay with a median of 15 versus 9 days in the DAP/CFT and RIF-Adj group, respectively ($P = .035$). Although in-hospital mortality was not significantly different between groups, 3 of the 4 documented mortalities were ICU patients from the RIF-Adj group that did not achieve defervescence nor symptom improvement.

There were no infection-related readmissions associated with the DAP/CFT group compared with 9 readmissions in the RIF-Adj group. Minimal adverse effects were identified with either regimen. No cases of nosocomial *C difficile* infection were observed. All secondary outcomes data are presented in Table 2.

DISCUSSION

To our knowledge, this is the first observational study comparing treatment of staphylococcal device infections with DAP/CFT versus RIF-Adj therapy. Despite all patients in the DAP/CFT group previously failing antimicrobial therapy, the resultant comparable clinical outcomes may support the use of this antibiotic combination as a salvage or alternative option.

Evidence demonstrating the potential clinical benefits of this synergistic regimen primarily in *S aureus* bacteremia is continuing to emerge. Geriak et al [5] aborted their study early due to a significant mortality reduction with DAP/CFT over monotherapy. A review article also reported successful use of daptomycin plus beta-lactams as salvage therapy for relapsing methicillin-resistant *S aureus* bacteremia [6]. However, 2 larger studies failed to demonstrate a clear benefit with this regimen over standard of care in this population [7, 8]. Although this was the conclusion in the study conducted by Fox et al [7], approximately half of their patients were switched to DAP/CFT due to persistently positive blood cultures potentially related to

Table 2. Outcomes

Outcomes	DAP/CFT (n = 6)	RIF-Adj (n = 31)	*P* Value
Clinical Success [patients, n (%)]	5 (83)	24 (77)	1.00
WBC normalization	5 (83)	25 (81)	
Sustained defervescence	6 (100)	28 (90)	
Symptom improvement	5 (83)	26 (84)	
In-hospital mortality [patients, n (%)]	1 (17)	3 (10)	0.524
Length of hospital stay [days; median (IQR)]	15 (5)	9 (8)	0.035
Infection-related readmission [patients, n (%)]			
30-day	0	6 (21)	0.562
90-day	0	9 (32)	0.303
Duration of antibiotic therapy [days; mean ± SD][a]	24 ± 18	39 ± 11	0.113
Adverse effects [patients, n (%)]			1.00
CPK elevation	0	1 (3)	
Transaminitis	0	0	
Peripheral eosinophilia	0	0	
Agranulocytosis	0	0	
Leukopenia	1 (17)	2 (6)	
Nosocomial *Clostridioides difficile* infection [patients]	0	0	1.00

Abbreviations: CPK, creatinine phosphokinase; DAP/CFT, daptomycin/ceftaroline; IQR, 25%–95% interquartile range; RIF-Adj, rifampin-adjunct; SD, standard deviation; WBC, white blood cell.

[a]Planned duration of antibiotic therapy upon discharge.

the significant higher baseline presence of hardware infection in the DAP/CFT compared with vancomycin group (43% vs 12%, $P = .0014$). Nevertheless, clinical outcomes were comparable, which demonstrates the utility of DAP/CFT as salvage therapy. The present study built upon this finding by comparing this regimen with standard staphylococcal device infection therapy. Likewise, DAP/CFT was highly successful as salvage therapy.

Baseline differences such as increased APACHE II and Charlson comorbidity index scores in this study may suggest more acutely ill and medically complex patients in the DAP/CFT group; correspondingly, lower scores in the RIF-Adj group may have favored positive outcomes. This may have contributed to the prolonged length of stay seen in the DAP/CFT group. Nonetheless, the lack of major differences across the rest of assessed clinical outcomes, including adverse drug reactions, add to the evidence that DAP/CFT is a valid alternative to RIF-Adj. In patients with drug interactions, such as anticoagulants, or contraindications to rifampin, DAP/CFT may therefore be a comparable substitute.

There are inherent limitations in a retrospective observational study design including unaccounted confounding variables and selection bias. The major limitation of this study was a small sample size with inadequate power to detect a difference in the primary outcome. Additional limitations include availability of laboratory tests and documentation—achieving symptom improvement was dependent on physician documentation in charts; potential for underestimating the incidence of adverse effects since identification of adverse effects was restricted to the laboratory tests ordered; and identification of infection-related readmissions was limited to those within the study hospital market.

CONCLUSIONS

The results of this study add to the mounting literature supporting the efficacy and safety of synergistic DAP/CFT in refractory staphylococcal infections. Specifically, DAP/CFT may be a useful alternative to or salvage therapy for RIF-Adj regimens in staphylococcal device infections, although more data are needed to elucidate a clear place in therapy.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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References

1. Barber KE, Werth BJ, McRoberts JP, Rybak MJ. A novel approach utilizing biofilm time-kill curves to assess the bactericidal activity of ceftaroline combinations against biofilm-producing methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **2014**; 58:2989–92.
2. Liu C, Bayer A, Cosgrove SE, et al.; Infectious Diseases Society of America. 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:e18–55.
3. Jacqueline C, Caillon J. Impact of bacterial biofilm on the treatment of prosthetic joint infections. J Antimicrob Chemother **2014**; 69 (Suppl 1):i37–40.
4. Rifadin® [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S., LLC; **2010**.
5. Geriak M, Haddad F, Rizvi K, et al. Clinical data on daptomycin plus ceftaroline versus standard of care monotherapy in the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2019**; 63:e02483–18.
6. Dhand A, Sakoulas G. Daptomycin in combination with other antibiotics for the treatment of complicated methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Ther **2014**; 36:1303–16.
7. Fox M, Zeqollari K, Lee G, et al. Daptomycin/ceftaroline in combination vs. vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Open Forum Infect Dis **2018**; 5 (Suppl 1):S318.
8. Grillo S, Cuervo G, Carratalà J, et al. Impact of β-lactam and daptomycin combination therapy on clinical outcomes in methicillin-susceptible *Staphylococcus aureus* bacteremia: a propensity score-matched analysis. Clin Infect Dis **2019**; 69:1480–8.