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Authors

Nigo, Masayuki
Diaz, Lorena
Carvajal, Lina P
et al.

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Ceftaroline-Resistant, Daptomycin-Tolerant, and Heterogeneous Vancomycin-Intermediate Methicillin-Resistant *Staphylococcus aureus* Causing Infective Endocarditis

Masayuki Nigo,[a] Lorena Diaz,[b,c] Lina P. Carvajal,[b] Truc T. Tran,[a,c] Rafael Rios,[b] Diana Panesso,[a,b,c] Juan D. Garavito,[b] William R. Miller,[a,c] Audrey Wanger,[e] George Weinstock,[f] Jose M. Munita,[a,b,c,d] Cesar A. Arias,[a,b,c] Henry F. Chambers (Commentator)[g]

Department of Internal Medicine, Division of Infectious Diseases, University of Texas Medical School at Houston, Houston, Texas, USA[a]; Molecular Genetics and Antimicrobial Resistance Unit, International Center for Microbial Genomics, Universidad El Bosque, Bogotá, Colombia[b]; Center for Antimicrobial Resistance and Microbial Genomics, University of Texas McGovern Medical School, Houston, Texas, USA[c]; Department of Medicine, Clínica Alemana de Santiago, Universidad del Desarrollo, Santiago, Chile[d]; Department of Pathology and Laboratory Medicine, University of Texas Medical School at Houston, Houston, Texas, USA[e]; The Jackson Laboratory for Genomic Medicine, Farmington, Connecticut, USA[f]; Department of Medicine, Division of HIV, Infectious Diseases and Global Medicine, Zuckerberg San Francisco General Hospital, University of California San Francisco, San Francisco, California, USA[g]

This journal section presents a real, challenging case involving a multidrug-resistant organism. The case authors present the rationale for their therapeutic strategy and discuss the impact of mechanisms of resistance on clinical outcome. An expert clinician then provides a commentary on the case.

ABSTRACT We report a case of infective endocarditis (IE) caused by ceftaroline-resistant, daptomycin-tolerant, and heterogeneous vancomycin-intermediate methicillin-resistant *S. aureus* (MRSA). Resistance to ceftaroline emerged in the absence of drug exposure, and the E447K substitution in the active site of PBP2a previously associated with ceftaroline resistance was identified. Additionally, we present evidence of patient-to-patient transmission of the strain within the same unit. This case illustrates the difficulties in treating MRSA IE in the setting of a multidrug-resistant phenotype.

KEYWORDS endocarditis, *Staphylococcus aureus*, ceftaroline

Infective endocarditis (IE) due to methicillin-resistant *Staphylococcus aureus* (MRSA) is a life-threatening infection for which vancomycin (VAN) has long been considered the drug of choice. However, its effectiveness has been questioned due to the emergence of *S. aureus* strains with reduced susceptibility to VAN (VAN-intermediate *S. aureus* [VISA] or heterogeneous resistance [hVISA]). Daptomycin (DAP) is a lipopeptide antibiotic with reliable *in vitro* bactericidal activity that is frequently used to treat invasive MRSA infections, including IE. Unfortunately, the emergence of DAP nonsusceptibility during therapy threatens its efficacy against severe MRSA infections, especially in the setting of decreased susceptibility to vancomycin (1). Among other alternatives, ceftaroline (CPT), a β-lactam with high affinity for penicillin-binding protein 2a (PBP2a), has been successfully used as salvage therapy for recalcitrant MRSA bacteremia and IE and has emerged as an interesting drug to manage these infections (2). However, recent reports of CPT-resistant MRSA isolates also threaten the clinical utility of this drug (3).

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Address correspondence to Cesar A. Arias (case author), cesar.arias@uth.tmc.edu, or Henry F. Chambers (commentator), henry.chambers@ucsf.edu.

TABLE 1 Susceptibility profiles of isolates from both patients

Antimicrobial(s)	MIC (μg/ml) for isolate[a]: IE	VAP	Interpretation (CLSI breakpoint MIC [μg/ml])[b]
Vancomycin	2*	2*	S (≤2)
Daptomycin	1*	1*	S (≤1)
Ceftaroline	4*	6*	R (≤1)
Clindamycin	>4	>4	R
Erythromycin	>4	>4	R
Gentamicin	>8	>8	R
Levofloxacin	>4	>4	R
Oxacillin	>2	>2	R
Linezolid	1	1	S
Rifampin	≤1	≤1	S
Tetracycline	≤1	≤1	S
TMP-SMX[c]	≤0.5/9.5	≤0.5/9.5	S

[a]IE, infective endocarditis; VAP, ventilator-associated pneumonia; *, MIC was determined with the Etest.
[b]S, susceptible; R, resistant.
[c]TMP-SMX, trimethoprim-sulfamethoxazole.

CASE PRESENTATION

The patient is a 36-year-old man without significant past medical history who was admitted to the burn unit after a motor vehicle accident resulting in burns of 28% of body surface. On day 46 of admission, the patient developed fever (102°F), and blood cultures yielded MRSA (VAN MIC, 1 μg/ml). The patient was started on VAN (1 g every 8 h), and a transesophageal echocardiogram revealed a 0.8- by 0.5-cm vegetation on the aortic valve. On day 7 of VAN therapy (trough levels between 15 and 20 μg/ml), blood cultures remained positive, and the patient developed an acute myocardial infarction attributed to an embolic occlusion of the coronary artery due to septic emboli. VAN was stopped, and therapy was switched to DAP (8 mg/kg body weight daily) plus CPT (600 mg every 8 h). The MICs of the isolate recovered from the bloodstream before the change of therapy were 2, 1, and 4 μg/ml for VAN, DAP, and CPT, respectively (Table 1). The patient rapidly improved after starting the new regimen, blood cultures cleared after 24 h, and he completed 6 weeks of combination therapy without recurrence of the bacteremia. Seven days after the onset of bacteremia in the patient described above, a 60-year-old man who had been admitted to the same unit with burns encompassing 55% of the body surface was diagnosed with ventilator-associated pneumonia (VAP). The organism recovered from bronchoalveolar lavage (BAL) fluid was an MRSA isolate that was also found to have a CPT MIC above the established clinical breakpoint (6 μg/ml) (Table 1). The patient was treated with VAN monotherapy with clinical improvement.

CHALLENGE QUESTION

What is the rationale for using the combination of DAP plus CPT in the treatment of recalcitrant infections caused by MRSA?

A. Development of reduced susceptibility to DAP is associated with an increase in susceptibility to β-lactams that target penicillin-binding protein 1 (PBP1).

B. CPT has intrinsic activity against MRSA.

C. β-Lactams seem to increase the binding of DAP to the cell membrane target.

D. The increased susceptibility to β-lactams has also been identified in hVISA and VISA MRSA strains that exhibit similar phenotypic characteristics to strains that have reduced susceptibility to DAP.

E. All of the above.

TREATMENT AND OUTCOME

High-inoculum MRSA infections and exposure to VAN are well-known risk factors for the development of the VISA/hVISA phenotype (4). Additionally, VISA/hVISA isolates have been shown to concomitantly exhibit decreased DAP susceptibility and to share

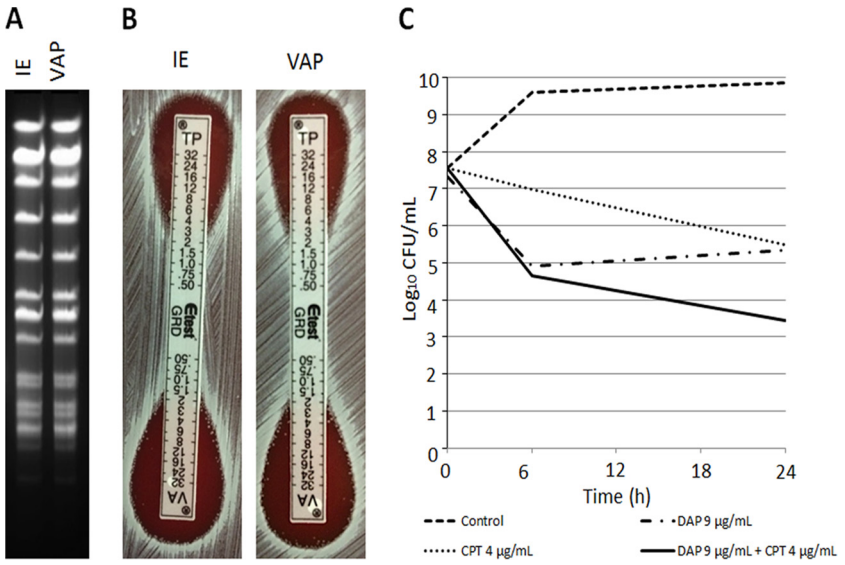

FIG 1 PFGE, GRD test, and killing curves for *S. aureus* isolates. (A) SmaI restriction-PFGE results for the IE and VAP strains show identical patterns. (B) Result of GRD test for IE and VAP strains after 48 h of incubation. (C) Time-kill assays for the CPT-resistant hVISA IE strain. The CPT-resistant hVISA IE strain was grown in Mueller-Hinton broth (MHB) supplemented with DAP (9 μg/ml) alone, CPT (4 μg/ml) alone, or the DAP-CPT combination and in the absence of DAP and CPT. DAP alone and CPT alone failed to show bactericidal activity, defined as $\geq$3-$\log_{10}$-CFU/ml reduction at 24 h in comparison to the initial inoculum. However, the combination restored the bactericidal activity and showed synergistic effects ($\geq$2-$\log_{10}$-CFU/ml reduction at 24 h in comparison to each antibiotic alone). The limit of detection was 10 CFU/ml. IE, infective endocarditis, VAP, ventilator-associated pneumonia; MHA, Mueller-Hinton agar, TP, teicoplanin.

common genetic pathways leading to tolerance to both of these compounds (5). In our case, the unexpected finding of CPT resistance left us with very few options to treat this patient. The combination of DAP and β-lactam antibiotics has shown synergism against MRSA, despite having β-lactam MICs out of the susceptible range (6). We decided to discontinue VAN and initiate a combination of DAP (8 mg/kg daily) plus CPT (600 mg every 8 h), which resulted in clinical success.

Due to the unexpected presence of CPT resistance and possibility of patient-to-patient transmission, we characterized the CPT-resistant *S. aureus* isolates recovered from the IE case and subsequent VAP patient. A detailed description of the methods is included in the supplemental material. The isolates obtained from both patients showed identical pulsed-field gel electrophoresis (PFGE) patterns (Fig. 1A) and antibiotic susceptibilities (Table 1). Screening of hVISA by the glycopeptide resistance detection (GRD) Etest was positive for both strains (Fig. 1B), and population analyses showed a subpopulation growing at a VAN concentration of 3 μg/ml (as is usually observed with hVISA strains). However, the calculated ratio of PAP to area under the concentration-time curve (AUC) compared to strain Mu3 was $\leq$9 (see Fig. S1 and Table S3 in the supplemental material). DAP and CPT were bacteriostatic in time-kill assays, but the combination of both antibiotics was synergistic, achieving bactericidal activity against the *S. aureus* strain recovered from the bloodstream of the IE patient (Fig. 1C). Whole-genome comparison of the strains showed the presence of 144 single nucleotide polymorphisms (SNPs) that differed between the isolates, suggesting that they were closely related strains. Additionally, both harbored SCC*mec* II *agr* type II and belonged to sequence type 105 (ST105) by multilocus sequence typing (MLST) (clonal complex 5). The analysis of resistomes predicted resistance to 5 antibiotic families and was concordant with the clinical susceptibility report (see Table S1 in the supplemental material). We found no genetic changes previously associated with DAP or VAN resistance or tolerance (see Table S2 in the supplemental material). In terms of CPT resistance, both isolates exhibited the E447K amino acid substitution in the predicted

PBP2a protein encoded by the *mecA* gene. No other changes previously related to CPT resistance were found.

In a single case, we illustrate the difficulties in treating MRSA IE when resistance emergences during therapy, showing the immense adaptability and plasticity of these multidrug-resistant organisms. The most striking feature of our case is the emergence of CPT resistance without exposure to the antibiotic and the ability of CPT-resistant organisms to be transmitted from patient to patient. Previous reports of CPT resistance emerging during therapy have been associated with the use of this antibiotic—sometimes for prolonged periods of time (3)—and to the best of our knowledge, emergence of resistance in the absence of CPT exposure has not been consistently documented. Our isolates harbored the E447K substitution in the predicted active site of PBP2a, which is one of the signature changes associated with CPT resistance (3). No changes in the allosteric domain of PBP2a or in other proteins previously involved in PBP2a-independent routes leading to CPT resistance were found (7). Our case raises the intriguing possibility that CPT resistance may be selected by β-lactams other than CPT. Particularly, our patient was previously exposed to piperacillin-tazobactam and cefepime. Another alternative is that the patient may have been colonized by a CPT-resistant strain, although this possibility is unlikely since he did not have a medical history suggestive of multiple contacts with the health care system. Importantly, CPT resistance emerged in the setting of decreased susceptibility to both VAN and DAP, suggesting that mutations in PBP 2a affecting CPT activity can be acquired in the setting of alterations in cell envelope homeostasis that mediate nonsusceptibility to VAN and DAP, posing an important therapeutic challenge. The fact that this multidrug-resistant MRSA isolate could be transmitted to another patient suggests that development of resistance did not markedly affect its fitness and the ability to spread from one host to the other. Additionally, the fact that the organism was capable of producing a different infection in a new patient suggests that no loss of virulence occurred, despite the expression of multiple resistance determinants.

The combination of DAP plus CPT has been shown to be synergistic *in vitro* against DAP-nonsusceptible strains of *S. aureus*. Exposure to β-lactams in such strains seems to increase the activity of DAP by favoring the binding of the antibiotic to the cell membrane (8). In a recent retrospective report, Sakoulas et al. analyzed 10 cases of MRSA IE and 2 cases of VISA infections (1 IE and 1 bacteremia) in which the combination of DAP plus CPT was successfully used. Of note, 2 cases included were DAP resistant, and one was an IE case due to MRSA with intermediate susceptibility to CPT (MIC, 2 μg/ml) (9). The management of our IE case was particularly complicated by the fact that the isolate was hVISA (and the patient failed VAN therapy) and was also shown to be DAP tolerant. Thus, additional CPT resistance significantly limited the therapeutic options. Despite the resistance phenotypes, we decided to use the combination of DAP plus CPT, taking theoretical advantage of the "seesaw" effect (10, 11). This rationale was strongly supported by our time-kill studies, which showed synergism using concentrations of antibiotics achievable by standard human dosing of both DAP and CPT. Moreover, recent studies have suggested that PBP1 plays an important role in this synergism, (12) and CPT has high affinity for *S. aureus* PBP1 (13). The clinical response was excellent, and we were able to complete therapy and successfully treat the patient without evidence of recurrence to date.

In summary, CPT resistance in the background of other multidrug-resistant phenotypes is a serious concern for the treatment of IE. Combination therapy seems to be effective against these organisms and should be seriously considered in the presence of multiple resistances.

COMMENTARY

The two patients with nosocomial infections reported by Nigo et al. from a hospital in Houston, one with endocarditis and one with ventilator-associated pneumonia, are a microcosm of a world of problems caused by methicillin-resistant *Staphylococcus aureus* (MRSA). These infections were caused by two very closely related sequence type

5 (ST5) multiple-drug resistant strains of the USA100 clone type, endemic in U.S. hospitals for over 30 years and still the most common type. The primary source and the mode of transmission of these strains are otherwise obscure and typical. Both strains had acquired resistance to ceftaroline due to a single canonical point mutation in *mecA* (3, 14, 15) under mysterious circumstances since neither patient had been previously treated with this antibiotic. It is of more than passing interest that the one other well-documented case of infection with ST5 ceftaroline-resistant MRSA was also identified in a Houston hospital 3 years earlier (3). In this case, there was a history of prior therapy with ceftaroline.

The report on a patient with endocarditis by Nigo et al. failed to clear the bacteremia with vancomycin, despite a vancomycin MIC of 1 μg/ml for the first blood isolate. The day 7 isolate had a vancomycin MIC of 2 μg/ml, a worrisome development as this occurred on therapy. Whether this was the cause or an effect of treatment failure is uncertain, particularly given that the patient with ventilator-associated pneumonia caused by a virtually identical isolate with a vancomycin MIC of 2 μg/ml responded to vancomycin. The importance of vancomycin MICs of $>$1 mg/ml as a predictor of treatment failure (16–28) has been hotly debated. In neither of these cases was the MIC a particularly good predictor. The patient whose initial isolate had a MIC of 1 μg/ml failed, whereas the patient whose initial isolate had a MIC of 2 μg/ml was cured.

What should be done when the patient is failing first-line therapy and choices are limited, as in the patient with endocarditis? The isolate was multiple-drug resistant, and although the daptomycin MIC was within the susceptible range, it was at the upper limit. Moreover, emergence of daptomycin resistance (technically, nonsusceptibility, but let us not mince words) on therapy does occur, may be preceded by prior therapy with a glycopeptide, and tracks with high-inoculum infections and intermediate susceptibility to vancomycin (i.e., VISA) (29, 30), including the rather ill-defined and difficult-to-test-for hVISA phenotype. The isolate did not meet strict criteria for either, but the distinction is academic given the persistently positive blood cultures, an increase in the MIC from 1 to 2 μg/ml, and a population analysis profile that just fell short of the Mu3 reference strain. These observations underscore limitations of *in vitro* susceptibility testing of vancomycin and argue against relying on the MIC alone for changing therapy. The choice of combination therapy with daptomycin given at 8 mg/kg once daily plus ceftaroline at 600 mg every 8 h was a reasonable one given the concern for emergence of resistance to daptomycin if used as a single agent. Ceftaroline alone was not an option because of resistance, but a β-lactam, even if there is resistance, in combination with daptomycin enhances binding of daptomycin to the bacterial cell membrane and synergistically potentiates its bactericidal effect (31–34). A theoretical added benefit is that each drug protects against emergence of higher-level resistance to the other by the seesaw effect (31), in which increasing resistance to one drug is counterbalanced by increasing susceptibility to the other. Rapid sterilization of the blood and eventual cure of the patient with endocarditis add to the admittedly anecdotal, but nevertheless compelling, data that daptomycin-ceftaroline combination therapy is an effective salvage regimen (9). Should such a regimen be used routinely as initial therapy for treatment of MRSA bacteremia and endocarditis? This question is best answered by a randomized clinical trial to determine whether outcomes are better for combination compared to single-drug therapy.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01235-16.

TEXT S1, PDF file, 0.4 MB.

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