JAC Antimicrob Resist
doi:10.1093/jacamr/dlab148

JAC-Antimicrobial Resistance

Oxacillin plus ertapenem combination therapy leads to rapid blood culture clearance and positive outcomes among patients with persistent MSSA bacteraemia: a case series

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Received 12 July 2021; accepted 2 September 2021

Background: Bloodstream infections caused by MSSA are associated with significant morbidity and mortality. Traditional treatment of MSSA bacteraemia includes an IV antistaphylococcal β-lactam and surgical source control when indicated.

Objectives: To evaluate the time to blood culture clearance as well as in-hospital and 90 day mortality in patients with persistent MSSA bacteraemia treated with combination antistaphylococcal penicillin plus carbapenem therapy.

Methods: Consecutive patients with persistent MSSA bacteraemia treated with combination therapy were identified by study investigators and reviewed by independent clinicians. The decision to initiate combination therapy was made by the consulting clinician or by the institution's multidisciplinary endocarditis team.

Results: Among 10 patients with a median of 5 days of persistent MSSA bacteraemia, treatment with an antistaphylococcal penicillin plus carbapenem led to sterilization of blood cultures in all patients. Blood culture clearance occurred in a median of 1 day and patients received a median of 6 days of combination treatment. Four of seven patients who underwent source control of their primary site of infection cleared their bacteraemia on combination therapy prior to the surgical intervention. All patients survived to hospital discharge and 90 days post-discharge.

Conclusions: These data extend prior findings and provide further evidence that suggests the potential benefits of combination therapy among patients with persistent MSSA bacteraemia.

Introduction

Bloodstream infections caused by MSSA are associated with significant morbidity and mortality.[1] One-third of patients develop invasive complications including septic arthritis, osteomyelitis, epidural abscesses and endocarditis.[2,3] Mortality rates among those with endocarditis are as high as 40%.[1] Traditional treatment of MSSA bacteraemia includes an IV antistaphylococcal β-lactam and surgical source control when indicated.[4,5] Despite these measures, ∼15% of patients experience persistent bloodstream infections for >7 days.[6–8] Moreover, many patients are not candidates for surgical management of infectious complications. Thus, new therapeutic approaches against MSSA bacteraemia are needed to limit complications and lower mortality. Recent reports have documented encouraging outcomes for patients with persistent MSSA bacteraemia treated with cefazolin and ertapenem combination therapy.[7,9] Here, we report our experience in managing 10 consecutive cases of MSSA bacteraemia treated with dual β-lactam combination therapy, prioritizing oxacillin in combination with a carbapenem.

Methods

Patient cases

Institutional review board exemption was obtained from the University of Pittsburgh and informed consent was not required of patients. Consecutive patients with persistent MSSA bacteraemia treated with combination therapy were identified by study investigators. Combination therapy was defined as the use of two antistaphylococcal β-lactams for ≥48 h as definitive treatment for MSSA bacteraemia. No patients who received β-lactam combination therapy were excluded over the study period. The decision to initiate combination therapy was made by the consulting clinician or by the

institution's multidisciplinary endocarditis team. All patients started on combination therapy had positive blood cultures upon treatment initiation. Patient charts were reviewed retrospectively by two independent investigators who were not involved in patient management.

Definitions

The duration of bacteraemia was defined by the number of days that elapsed between the first positive blood culture and two consecutive negative blood cultures, or a single negative blood culture if only one was obtained. Days for which no blood cultures were collected were presumed positive unless there was a prior negative blood culture.[10] Persistent bacteraemia was defined as a positive follow-up blood culture collected >2 days after the first positive blood culture.[10] Days to blood culture clearance were defined by the number of days that elapsed between initiation of combination therapy and documentation of negative blood cultures. Patients without evidence of active infection 90 days after their index infection were presumed to be infection free.

Antimicrobial susceptibility and synergy testing

Index bloodstream isolates were collected and tested for susceptibility to oxacillin, ertapenem and meropenem by standard broth microdilution methods in duplicate. Sodium chloride was added to cation-adjusted Mueller–Hinton broth as recommended by CLSI. *Staphylococcus aureus* ATCC 29213 was used for quality control throughout; results were interpreted according to CLSI breakpoints. To identify *in vitro* synergy, oxacillin was tested in combination with ertapenem and meropenem by chequerboard assays. Synergy was defined as an FIC index <0.5 as previously described.[7]

Results

Between 17 August 2020 and 12 March 2021, 151 unique patients with *S. aureus* bacteraemia were identified. Fifty-six percent (85/151) of patients were infected with MSSA. The overall median duration of MSSA bacteraemia was 1 day (range: 1–11 days) and 27% (23/85) of cases met our criteria for persistent bacteraemia. Overall, 10 cases of persistent MSSA bacteraemia were treated with β-lactam combination therapy (Table 1). The median age was 32 years and 8 were women. Median Charlson Comorbidity Index and Pitt bacteraemia scores were 1.5 (range: 1–4) and 0.5 (0–4), respectively. Seven cases were associated with infective endocarditis; six of which had vegetations identified by echocardiogram and one patient without a vegetation met modified Duke criteria for definite endocarditis (Case 9).[11] Of the remaining cases, two were complicated by epidural abscesses and one by osteomyelitis and mediastinitis. Overall, seven patients were admitted to intensive care at the time of diagnosis.

All patients were initiated on *in vitro* active therapy (i.e. vancomycin) empirically within 15 h of index blood culture collection before de-escalation to a targeted antistaphylococcal β-lactam. Oxacillin was selected as initial MSSA-targeted therapy in nine cases. In total, patients received a median 3 days of targeted therapy prior to combination treatment. At the initiation of combination therapy, the median duration of bacteraemia was 5 days (range: 3–8 days). Oxacillin plus ertapenem was started in seven cases. In the remaining three cases, cefazolin plus ertapenem was used in the setting of a penicillin allergy (Case 2), oxacillin was switched to nafcillin for a patient experiencing increased liver function tests (LFTs) prior to combination therapy (Case 6) and oxacillin plus meropenem was used for one patient with hypoalbuminaemia (Case 8).[12]

Blood cultures were sterilized in all cases; six patients had documented clearance within 1 day and nine had documented clearance based on the first blood culture obtained following the initiation of combination therapy. Combination treatment was continued for a median of 6 days (range: 2–10 days) at which point carbapenems were discontinued in all cases. Source control was pursued in all three non-endocarditis cases by abscess drainage and debridement. In four of seven endocarditis cases, source control was achieved with valve repair/replacement. In four of seven patients who underwent definitive source control, blood cultures cleared on combination therapy prior to source control being achieved. Surgical valve cultures were collected in three patients and were positive for one (Case 8). All patients survived to hospital discharge. Two recurrent events were identified following discharge, including subsequent MSSA bacteraemia in a patient with ongoing injection drug use (Case 3) and one patient with a persistent epidural abscess who received only 2 days of combination therapy (Case 6). All patients were alive at 90 days following the onset of MSSA bacteraemia.

Overall, combination therapy was well tolerated. Following treatment initiation, three patients were switched from oxacillin to cefazolin due to increased LFTs, rash or to limit total parenteral volume. The median duration of antimicrobial therapy was 48 days. Rifampicin was added after carbapenems were discontinued in two patients with indwelling prosthetic material.

MSSA isolates demonstrated median oxacillin, ertapenem and meropenem MICs of 0.5 (range: 0.25–1 mg/L), 0.25 (0.12–0.25 mg/L) and 0.25 (0.12–0.25 mg/L), respectively. One isolate showed *in vitro* synergy to the combination of oxacillin and ertapenem or meropenem. Additive activity (FIC index between 0.51 and 0.99) was confirmed for all other isolates. The median FIC index for oxacillin plus ertapenem or meropenem was 0.61 and 0.66, respectively.

Discussion

In this case series we report our experience in successfully managing 10 consecutive patients with persistent MSSA bacteraemia who were treated with combination β-lactam therapy. Combination treatment was initiated following a median of 5 days of persistent bacteraemia and repeat blood cultures cleared in all patients at a median of 1 day. All patients survived to our long-term follow-up endpoint of 90 days and recurrent infections were infrequent. Seven of 10 patients had definite endocarditis.[11] MSSA was not cultured from the excised valve/vegetations in two of three patients who underwent valve surgery, which allowed for shorter durations of antibiotic therapy post-operatively. Importantly, decisions regarding initiating dual β-lactam therapy for endocarditis patients were made by a multidisciplinary endocarditis team.[13] Taken together, our data extend those recently presented by Ulloa and colleagues[7] who showed positive clinical outcomes among 11 patients with persistent MSSA bacteraemia treated with cefazolin and ertapenem. Here, oxacillin plus a carbapenem was prioritized, suggesting that combination β-lactam therapy can be successfully employed with either an antistaphylococcal penicillin or cefazolin in combination with ertapenem. These new insights are noteworthy given the association between

Table 1. Clinical characteristics and treatment outcomes of patients with persistent MSSA bacteraemia treated with combination therapy

Case	Age/ Sex	Comorbidities	CCI	ICU[a]	PBS	Source(s) of BSI (size of vegetation)	Tx (duration, days)			Duration of BSI (days)		Source control (duration of BSI afterwards, days)	Definitive Tx (total duration, days)	Clinical outcome and comments
							empirical	targeted	combo	pre-combo Tx	post-combo Tx			
1	32/F	HCV, PWID	1	Yes	1	Native TV IE (1.4 × 2.6 cm)	FEP (2) VAN (3)	OXA (4)	OXA + ETP (5)	6	1	TV repair on hospital Day 6 (2)	OXA (34)	Survived to hospital discharge and infection free at Day 90.
2	23/F	HCV, PWID, bipolar disorder	1	No	0	Native TV IE (2.7 cm)	FEP (3) VAN (3)	CFZ (1)	CFZ + ETP (9)	3	2[b]	TV repair on hospital Day 9 (N/A; cleared on combo therapy)	CFZ (32)	Survived to hospital discharge and infection free at Day 90.
3	32/M	HCV, PWID	1	Yes	2	Prosthetic TV IE (1.1 × 1.3 cm)	TZP (1) VAN (1)	OXA (3)	OXA + ETP (9)	5	1	None	OXA (47) RIF (31)[c]	Survived to hospital discharge. Developed recurrent MSSA IE 32 days after discharge in the setting of ongoing injection drug use.
4	26/F	HCV, PWID, preeclampsia, asthma	1	No	0	Native PV IE (2.4 × 0.9 cm)	N/A	OXA (3)	OXA + ETP (5)	3[d]	1	None	OXA (11), then CFZ (46)	Survived to hospital discharge and infection free at Day 90. Switched from OXA to CFZ due to increasing LFTs.
5	28/F	HCV, PWID, PUD, depression	2	Yes	0	Native MV and TV IE (1.6 × 1.3 cm) (1.2 × 2.1 cm)	MEM (1) VAN (3)	OXA (3)	OXA + ETP (10)	5	2[b]	MV and TV replacement on hospital Day 25 (N/A; cleared on combo therapy)	OXA (49)	Survived to hospital discharge and infection free at Day 90. Course complicated by mycotic aneurysm and septic emboli.
6	64/F	HTN, RA, T2DM	4	Yes	3	Epidural abscess, septic arthritis	FEP (2) VAN (3)	OXA (3), then NAF (4)	NAF + ETP (2)	8	3	Psoas abscess drainage on hospital Day 29 Anterior lumbar debridement on hospital Day 32 Hardware removal and posterior lumbar debridement on hospital Day 35 (N/A; cleared on combo therapy)	OXA (3), then NAF (42), then CFZ (18) RIF (28)	Survived to hospital discharge. Developed recurrent epidural abscess 21 days after discharge. Switched from OXA due to CFZ due to increasing LFTs.
7	70/F	HLD, Afib	3	Yes	1	Vertebral OM, mediastinitis	TZP (2) VAN (2)	OXA (2)	OXA + ETP (6)	4	1	Mediastinal abscess drainage on hospital Day 2 (4)	OXA (11), then TZP (8), then OXA (59)	Survived to hospital discharge and infection free at Day 90. Transitioned to TZP to treat concurrent pneumonia.
8	22/F	PWID, T1DM	1	Yes	0	Native TV IE (3.0 × 2.5 cm)	TZP (3) VAN (3)	OXA (1)	OXA + MEM (4), then CFZ + MEM (4)	6	2[e]	TV replacement on hospital Day 4 (1)	OXA (5), then CFZ (42)	Survived to hospital discharge and infection free at Day 90. Course complicated by septic emboli. Switched from OXA to CFZ due to volume status concerns.
9	47/M	HTN, HLD, T2DM, CVA	2	Yes	4	Native MV IE	VAN (1)	OXA (1)	OXA + ETP (6)	3	1	None	OXA (10), then CFZ (35)	Survived to hospital discharge and infection free at Day 90.

Continued

Table 1. *Continued*

Case	Age/ Sex	Comorbidities	CCI	ICU[a]	PBS	Source(s) of BSI (size of vegetation)	Tx (duration, days)			Duration of BSI (days)		Source control (duration of BSI afterwards, days)	Definitive Tx (total duration, days)	Clinical outcome and comments
							empirical	targeted	combo	pre-combo Tx	post-combo Tx			
10	66/F	HTN, HLD, T2DM	3	No	0	Epidural abscess	FEP (2) VAN (2)	OXA (3)	OXA + ETP (6)	5	1	Abscess drainage and laminectomy on hospital Day 7 (N/A; cleared on combo therapy)	OXA (49)	No vegetation identified but met modified Duke criteria for definite endocarditis. Course complicated by mycotic aneurysm and septic emboli. Switched from OXA to CFZ due to rash. Survived to hospital discharge and infection free at Day 90.

Afib, atrial fibrillation; BSI, bloodstream infection; CCI, Charlson Comorbidity Index; CFZ, cefazolin; CVA, cerebrovascular accident; ETP, ertapenem; FEP, cefepime; HLD, hyperlipidaemia; HTN, hypertension; IE, infective endocarditis; RA, rheumatoid arthritis; MEM, meropenem; MV, mitral valve; N/A, not applicable; NAF, nafcillin; OM, osteomyelitis; OXA, oxacillin; PBS, Pitt bacteraemia score; PUD, peptic ulcer disease; RIF, rifampicin; TZP, piperacillin/tazobactam; PWID, person who injects drugs; PV, pulmonary valve; T1DM, type 1 diabetes mellitus; T2DM, type 2 Diabetes mellitus; TV, tricuspid valve; Tx, treatment; VAN, vancomycin.

[a]At the time of diagnosis of bloodstream infection.

[b]No blood cultures drawn on the day after combination treatment was initiated.

[c]Rifampicin added after ertapenem was discontinued.

[d]Patient was already known to have MSSA bacteraemia and had left against medical advice 1 week prior to returning to the hospital for further care. The start date of BSI in this case refers to first positive culture after returning for care and not to when cultures were initially positive during the first hospitalization.

[e]No blood cultures drawn until 2 days after combination treatment was initiated.

cefazolin inoculum effects and increased mortality among patients with MSSA bacteraemia.[14] On balance, cefazolin offers improved tolerability compared with oxacillin, which was also seen in our series.[15] While dual β-lactam therapy was well tolerated overall, carbapenems are known to have several toxicities including effects on patients' mental status. These potential adverse reactions may not have been captured given the small size of this case series.[16]

Mechanisms supporting the utility of β-lactam combination therapy have been proposed to include use of two agents with complementary binding of PBP sites that target multiple steps in cell wall synthesis, thereby providing enhanced bacterial killing.[7] Ertapenem and cefazolin demonstrate strong affinity for PBP1 and PBP2, respectively. Alternatively, most patients in our study were treated with oxacillin plus ertapenem. Oxacillin is believed to preferentially bind to PBP1 in MSSA; however, a previous study also showed increased expression of PBP2 and PBP3 in the presence of subinhibitory concentrations of oxacillin.[17] Thus, it is possible that oxacillin acts as a non-selective PBP inhibitor and demonstrates complimentary PBP binding with ertapenem. It is also possible that more complete saturation of PBP1 binding sites with the combination results in greater killing activity. Our *in vitro* synergy data provide a foundation for this hypothesis as additive activity was seen for all isolates when oxacillin was combined with either ertapenem or meropenem. Our median FIC index was comparable to those previously reported against the combination of ertapenem with cefazolin or nafcillin.[7] Meropenem may also be considered as an alternative for patients with hypoalbuminaemia where ertapenem exposures are suboptimal.[12]

Our study is limited by its retrospective, observational design, small sample size and absence of a control group managed with standard-of-care approaches. Additionally, 3 of the 10 patients received surgical source control prior to blood culture clearance, which may confound the impact of combination antibiotic therapy. Overall, our data are consistent with earlier reports of encouraging patient outcomes and are the first to demonstrate the efficacy of oxacillin and ertapenem against MSSA bacteraemia.[7,9] These studies provide a basis for future investigation, and in particular a randomized clinical trial comparing the efficacy for standard-of-care treatment versus β-lactam combination therapy for patients with persistent MSSA bacteraemia. A pragmatic design may also provide an opportunity to compare combination regimens and the duration of combination therapy, for which few data currently exist. The main benefit of combination therapy reported thus far is rapid clearance of blood cultures. This is noteworthy given that time to sterilization of blood cultures for patients with *S. aureus* bacteraemia, including endocarditis, may be associated with improved clinical outcomes and lower rates of death.[10] Until future studies can validate the potential benefit of β-lactam combination therapy weighed against the risk for toxicity and/or expanded use carbapenems in the hospital environment, consideration could be given to approaches that prioritize short durations of combination therapy early in the treatment course followed by de-escalation to the preferred antistaphylococcal agent once blood cultures are sterilized and sources of bacteraemia are controlled.[1–3,10]

Funding

The study was carried out as part of our routine work.

Transparency declarations

All authors contributed to the manuscript and have no conflicts of interest to disclose.

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