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Short communication

Use of ceftaroline after glycopeptide failure to eradicate meticillin-resistant *Staphylococcus aureus* bacteraemia with elevated vancomycin minimum inhibitory concentrations☆

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ABSTRACT

Elevated minimum inhibitory concentrations (MICs) of vancomycin against meticillin-resistant *Staphylococcus aureus* (MRSA) and the emergence of heteroresistant *S. aureus* strains have led to increased use of anti-MRSA antibiotics other than vancomycin. Ceftaroline fosamil is a novel cephalosporin with activity against MRSA, but there are limited clinical data on its use for MRSA bacteraemia (MRSAB) and against strains exhibiting high vancomycin MICs (2–4 μg/mL). This multicentre, retrospective, case–control study compared the microbiological and clinical effectiveness of ceftaroline used after vancomycin failure with that of vancomycin-treated controls for the treatment of MRSA with vancomycin MICs ≥ 2 μg/mL. In total, 32 patients were matched 1:1 with respect to vancomycin MIC, age and origin of bacteraemia. In the ceftaroline group, patients received prior MRSA therapy for a median of 5 days [interquartile range (IQR), 3–15.8 days] prior to switching to ceftaroline. Median time to eradication of MRSA was significantly less after treatment with ceftaroline compared with vancomycin [4 days (IQR, 3–7.5 days) vs. 8 days (IQR, 5.8–19.5 days); $P = 0.02$]. Both clinical success at the end of treatment and recurrence of MRSA at Day 7 were trending towards being inferior in the vancomycin group, although the results did not attain statistical significance [81% vs. 44% ($P = 0.06$) and 6% vs. 38% ($P = 0.08$), respectively]. Ceftaroline added at the point of vancomycin failure resolves MRSAB more rapidly and with a higher rate of clinical success, therefore ceftaroline should be considered as an alternative for these difficult-to-treat infections.

1. Introduction

Meticillin-resistant *Staphylococcus aureus* bacteraemia (MRSAB) is a growing clinical concern that is associated with significant morbidity and mortality [1]. Vancomycin remains the first-line treatment for infections caused by MRSA. The susceptibility breakpoint for vancomycin has been set at ≤2 μg/mL and on this basis the frequency of in vitro resistance to vancomycin remains low in most institutions. However, multiple reports have been published on the occurrence of elevated minimum inhibitory concentrations (MICs) among MRSA strains and the associated detrimental effect on the efficacy of vancomycin [2,3]. Indeed, a recent meta-analysis reported a vancomycin MIC ≥ 1 μg/mL as a factor independently predictive of treatment failure [odds ratio (OR) = 2.69, 95% confidence interval (CI), 1.60–4.51] and mortality among patients with MRSAB (OR = 1.58, 95% CI, 1.06–2.37) [4].

Adding to the concern with using vancomycin as first-line therapy for MRSAB is the emergence of heteroresistant vancomycin-intermediate *S. aureus* (hVISA) [5]. The frequency of hVISA has been shown to be MIC-dependent, with prevalence increasing steadily among strains with elevated MICs [6]. For MRSA

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isolates with elevated vancomycin MICs (≥1.5 μg/mL) or strains that harbour the hVISA phenotype, the treatment of choice remains unclear.

Ceftaroline, the active agent of the prodrug ceftaroline fosamil, is an extended-spectrum cephalosporin with activity against MRSA [7]. Use of ceftaroline in MRSAB and endocarditis with low vancomycin MICs has been described [8]. The objective of this study was to compare the time to pathogen eradication as well as the relationship with the time to clinical improvement between ceftaroline and case-matched high MIC (2–4 μg/mL) vancomycin-treated controls in the treatment of adults with MRSAB and other serious infections.

2. Materials and methods

2.1. Study design and sites

This was a retrospective, multicentre (Erie County Medical Center, Buffalo, NY; University of Pittsburgh Medical Center, Pittsburgh, PA; Oregon Health and Science University, Portland, OR; and Robert Wood Johnson Medical Center, New Brunswick, NJ), matched, case–control study conducted from November 2012 to August 2013. The institutional review boards (IRBs) at each of the participating medical centres approved the study. Owing to the retrospective nature of the data collection procedures, subject informed consent was not mandated by any of the IRBs.

2.2. Data collection

Pertinent demographic and clinical data were obtained from electronic medical records for all patients. Variables collected include age, sex, weight, empirical treatment, in vitro susceptibility, duration of all antibiotics active against MRSA, time to eradication (days) and length of hospital stay associated with initiation of antibiotics. Results of any follow-up cultures obtained and documented in the medical records were examined to determine whether MRSA was eradicated from the primary infection site and/or blood.

2.3. Study groups and analysis groups

Eligible case subjects were hospitalised patients aged ≥18 years identified with infections caused by MRSA (concomitant bacteraemia preferred) and treated with vancomycin (MIC = 2–4 μg/mL) initially then switched to ceftaroline (MIC ≤ 1 μg/mL), or placed on ceftaroline empirically. Additional inclusion criteria included clinical signs and symptoms of infection (body temperature >38 °C or <36.1 °C, white blood cell count >10 000 cells/mm^3 and >10% bands at baseline), radiological findings consistent with pneumonia (chest radiograph with progressive infiltrate or consolidation), or wound redness, swelling or purulence in the case of acute bacterial skin and skin-structure infection (ABSSSI). An eligible control subject included similar patients with MRSA (concomitant bacteraemia preferred), treated with vancomycin (MIC = 2–4 μg/mL), then continued on vancomycin or placed on an alternative antibiotic active against MRSA (excluding ceftaroline). Additional inclusion criteria included the clinical signs and symptoms or findings as described above. Controls were matched at a 1:1 ratio with cases, and matching parameters included vancomycin MIC, age (±15 years) and primary site of infection. For the purpose of matching, patients were placed into one of the following categories based on the primary source of bacteraemia: ABSSSI; endocarditis; osteomyelitis; pneumonia; complicated intra-abdominal infection; or automatic implantable cardioverter–defibrillator (AICD) infection.

Patients were excluded if bacteraemia was determined to be catheter-related with no definitive evidence of secondary source, if life expectancy was <3 months from the underlying disease, or patients who were on a prior antibiotic and showed clinical or microbiological cure before treatment with ceftaroline or vancomycin.

2.4. Definitions

MRSA bloodstream infection was defined as patients with MRSA in blood cultures (MRSAB) that met the US Centers for Disease Control and Prevention (CDC) criteria for bloodstream infection [9]. The concomitant site with MRSA infection was determined by assessment of other MRSA-positive cultures at the time of onset of MRSAB. In the ceftaroline group, MRSA therapy included vancomycin, daptomycin, linezolid, tigecycline and rifampicin preceding a switch to ceftaroline. The control group encompassed treatment with all MRSA therapies as described above (except for ceftaroline). Time to eradication was calculated from the first day of ceftaroline in the ceftaroline treatment group and from the first day of MRSA therapy in the control group. Total days to eradication was calculated from the first day of any anti-MRSA therapy in the ceftaroline and control groups. Infection-related length of hospital stay (LOS_{IR}) was calculated from the first day of antibiotic therapy for MRSAB until the last day of antibiotic therapy or discharge, whichever occurred first [10].

2.5. Microbiological response

A positive baseline infection site culture and/or blood culture provided the basis for evaluating microbiological results on the final day of anti-MRSA therapy or at discharge, whichever occurred first. Eradication was declared if MRSA was eliminated from the initial infection site during or upon completion of therapy. Eradication was presumed if the patient was improved clinically and there was an absence of appropriate material for culture or if further sampling of blood cultures was not clinically indicated. Time to eradication was calculated using the first day the causative pathogen was absent on repeat cultures, or when a presumed eradication was documented.

2.6. Clinical outcomes assessment

Patients were placed in three groups: (i) case patients treated with other MRSA therapy prior to ceftaroline; (ii) case patients in the time period after initiation of ceftaroline; and (iii) vancomycin-treated control patients. A pre-post assessment was performed to analyse case patients before and after ceftaroline use. A secondary comparison was done to assess the case patients versus vancomycin-matched controls.

Outcomes included clinical success and LOS_{IR}. Response was assessed for clinical success on the last day of antibiotic treatment [end of treatment (EOT)]. Success included cure or improvement. Cure was defined as complete resolution of all symptoms and signs of infection or a return to patient's baseline state, and improvement was defined as clear improvement but incomplete resolution of all pre-therapy symptoms, or signs of incomplete return to the patient's baseline status, with no further antibiotic treatment necessary. Failure was defined as persistence or progression of symptoms and signs of infection or any of the following: new clinical findings consistent with active infection; death due to infection; inability to complete study of antibiotic treatment due to adverse events; or treatment required with another antimicrobial regimen.

2.7. Statistical methods

Student's *t*-test or Mann–Whitney *U*-test were used to compare continuous variables. Categorical variables were compared by